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Extracorporeal Shockwave Lithotripsy Monotherapy for Large Renal Calculi

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Summary—Extracorporeal shockwave lithotripsy (ESWL) monotherapy with a Dornier HM3 lithotripter was used to treat 199 large (≥ 3 cm) renal calculi. Calculi were classified as solitary (29), multiple (152) or staghorn (18) with stone-free rates of 55.2, 39.5 and 55.6% respectively. The stone-free rate was not statistically related to stone size, site or multiplicity. Complications occurred in 24 patients (12.8%) and were more common with solitary and staghorn calculi. ESWL is not recommended as primary treatment for most patients with large renal calculi.

Extracorporeal shock-wave lithotripsy (ESWL) was introduced clinically in 1980, 8 years after renal calculi were successfully destroyed *in vitro* using shock waves (Hepp, 1972; Chaussy *et al.*, 1980). Together with percutaneous nephrolithotomy (PCNL), ESWL has revolutionised the treatment of symptomatic renal calculi to the point where anatrophic nephrolithotomy is now rarely performed. Initial clinical experience in Germany and elsewhere with ESWL was primarily confined to small calculi with stone-free results ranging from 44.1 to 90% (Chaussy and Schmiedt, 1983; Drach *et al.*, 1986; Lingeman *et al.*, 1986; Palfrey *et al.*, 1986; Politis and Griffith, 1987). ESWL monotherapy has been applied to only a small percentage of patients with large (≥ 3 cm) renal calculi, but the need for multiple treatments, the high incidence of adjunctive procedures required and the low stone-free outcome have prompted the recommendation that large calculi should be treated with combination PCNL-ESWL therapy (Lingeman *et al.*, 1986). We present the results of ESWL monotherapy for large renal calculi.

Patients and Methods

Data on all patients treated in this department with a Dornier HM3 lithotripter are stored electronically in a Digital 11/82 microcomputer using specifically customised File Manager Software. All calculi are staged according to number, site and size using the PICA/Burden system (Griffith and Valiquette, 1987). The data bank was searched for information on all kidneys with stones ≥ 3 cm treated with ESWL monotherapy. Kidneys which had previous PCNL were excluded from this study. Calculi were classified as solitary, multiple or staghorn.

Solitary and multiple calculi were subclassified according to site. Staghorn calculi were documented in the computer as solitary calculi with pelvic, infundibular and caliceal components. The relevant X-rays were reviewed to categorise the staghorns as borderline, partial or complete. Borderline staghorns fill the renal pelvis +1 calix, partial staghorns fill the renal pelvis ≥ 2 calices, and complete staghorns completely fill the renal collecting system. Staghorn calculi were chosen for ESWL monotherapy on the basis of absence of hydronephrosis and relative radiolucency of the calculi when compared to adjacent ribs.

Statistical analysis of data was performed using chi-squared testing.

Results

Radiological follow-up was available on 199 of 214 kidneys. There were 89 males and 99 females with a mean age of 51 years (range 20–92). Stone

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classification is outlined in Table 1. There were 29 solitary, 152 multiple and 18 staghorn calculi.

The stone size, number of ESWL treatments and the number of shocks administered are outlined in Table 2. The results of treatment were assessed on the basis of KUB ± intravenous urogram after a minimum period of 3 months from the time of the last ESWL treatment. Patients were categorised as stone-free or with residual stones (≤5 mm or >5 mm (Table 3).

With regard to solitary calculi, 5 patients (83%) with upper infundibulo-caliceal calculi and 7 (70%) with pelvic calculi became stone-free, whereas only 4 (33%) with lower infundibulo-caliceal calculi became stone-free. This difference was not statistically significant ($P=0.095$). The highest stone-free rates for multiple calculi were for those in the pelvis and calices (53%) and in the infundibula (42%), with an overall stone-free rate of 39.5%. Once more, statistical significance was not demonstrated ($P=0.196$). All patients with complete staghorns became stone-free, but only 4 (50%) with borderline and 3 (43%) with partial staghorns became stone-free ($P=0.228$).

Table 1 Classification, Number and Stone-free Results of Large Renal Calculi

Calculi	*Site*	*Number*	*No. stone-free (%)*
Solitary	Upper infundibulo calix	6	5 (83)
	Middle infundibulo-calix	1	0 (0)
	Lower infundibulo-calix	12	4 (33)
	Pelvis	10	7 (70)
Multiple	Caliceal	34	10 (29)
	Infundibular	12	5 (42)
	Pelvic	3	1 (33)
	Caliceal and infundibular	19	4 (21)
	Caliceal and pelvic	59	31 (53)
	Infundibular and pelvic	12	4 (33)
	Caliceal and infundibular and pelvic	13	5 (39)
Staghorn	Borderline	8	4 (50)
	Partial	7	3 (43)
	Complete	3	3 (100)
Total		199	86 (43)

Table 2 Details of Treatment

Calculi	*Stone size (mm)*	*No of treatments/kidney*	*No. of shocks/kidney (mean)*
Solitary	30–42 (34)	1.35	1050–3600 (2104)
Multiple	30–133 (49)	1.41	2000–5650 (3128)
Staghorn	35–160 (64)	1.28	2000–5000 (2995)

Table 3 Results of Treatment

		Residual stones	
Calculi	*Stone-free (%)*	*≤5 mm (%)*	*>5 mm (%)*
Solitary	16 (55.2)	7 (24.1)	6 (20.7)
Multiple	60 (39.5)	26 (17.1)	66 (43.4)
Staghorn	10 (55.5)	3 (16.7)	5 (27.8)
Total	86 (43.2)	36 (18.1)	77 (38.7)

Complications occurred in 24 patients (12.8%) and all were successfully treated (Table 4). Steinstrasse were managed with percutaneous nephrostomy in 6 patients, ureteroscopy in 3 and analgesia alone in 7. All pyrexias resolved with intravenous antibiotic administration. The 2 cases of hydronephrosis settled with conservative management and the 1 patient who had a respiratory arrest required ventilation for 24 h.

Discussion

Although <10% of our total ESWL practice deals with large renal calculi, it is important to document the outcome of treatment in order to assess objectively the various therapeutic options. There is little doubt that the results with the Dornier HM3 lithotripter will be used in the future as a baseline against which results of treatment with the various second and third generation lithotripters can be compared.

The importance of stone site in relation to stone-free outcome has been previously reported (Politis and Griffith, 1987; Gleeson *et al.*, 1988) and was once more confirmed in this study. With regard to large solitary calculi, only those in the renal pelvis and upper pole have stone-free rates following ESWL that approach results achieved with open surgical lithotomy or percutaneous nephrolithotomy.

The multiplicity of calculi has also been shown to have an adverse effect on the stone-free results of ESWL (Lingeman *et al.*, 1986; Gleeson *et al.*, 1988). The proposed theoretical advantage of

Table 4 Complications

Calculi	*Steinstrasse*	*Pyrexia*	*Hydronephrosis*	*Respiratory arrest*
Solitary	6	2	—	—
Multiple	6	2	2	—
Staghorn	4	1	—	1

ESWL monotherapy for multiple calculi was that PCNLwould require multiple percutaneous punctures of the kidney, and although a single tract has been shown to have no effect on renal function, multiple tracts may damage nephrons and reduce renal reserve (Webb and Fitzpatrick, 1985). Also, ESWL monotherapy—even with multiple treatment sessions—was perceived to be less morbid than PCNL. However, in this study of multiple large stones, the overall stone-free rate was 39.5% and even with multiple calculi in the most favourable sites (pelvis+calices), only 53% of kidneys became stone-free. This result is significantly less than can be achieved with percutaneous nephrostolithotomy (Lee *et al.*, 1986).

Following PCNL for patients with large stones, any large residual stone burden is usually in the form of multiple calculi. If the residual are ≥ 3 cm, the expectation of rendering the patient stone-free with ESWL is no better than that of ESWL monotherapy for a similar stone burden (unpublished data). In other words, the chance of "cleaning up" post-PCNL large residual stones is $<40\%$.

Although the mean size of staghorn calculi treated was larger than that of solitary calculi (64 versus 34 mm), the stone-free rates were similar. The relative radiolucency of staghorn calculi appears to increase the possibility of a stone-free outcome and give stone-free results similar to those of other series with ESWL monotherapy (Table 5). Fuchs and Chaussy (1987) have drawn attention to the fact that a normal renal collecting system is more likely to produce a stone-free result and this influenced our selection of staghorn patients.

The high incidence of complications with solitary calculi (27.6 and 33.3% respectively) is attributed to the infrequent use of ureteric stents at the start of the series. Routine stent placement in all patients with large calculi has now helped to decrease the incidence of steinstrasse (Shabsigh *et al.*, 1988).

Overall, the stone-free outcome of ESWL monotherapy of large renal calculi was 43% and was not statistically related to stone size, site or multiplicity.

ESWL monotherapy requires mechanical fragmentation of stones and biological excretion of fragments. Clinical experience has shown that stone fragments ≤ 4 mm pass successfully in more than 80% of cases. The low stone-free outcome achieved in this study resulted primarily from (1) failure of spontaneous passage of small particles that usually collect in the gravity-dependent caudal calices, and (2) refusal by patients to accept the inconvenience, morbidity and economic cost of additional ESWL procedures to pulverise the fragments > 5 mm. All of our patients with residual stones > 5 mm were offered repeat ESWL, but in the absence of persistent symptomatology, few accepted. Thus the limiting factors in ESWL monotherapy of large renal stones are the endurance of the patient, the economic cost of multiple procedures and the functional integrity of the collecting system.

We believe that ESWL is inappropriate primary treatment of many (perhaps most) patients with large stones. The relative outcome, risks and economic cost of the operative and non-operative alternatives must be taken into consideration for each individual patient before deciding upon treatment.

Table 5 Stone-free rates of Staghorn Calculi

Authors	*Percentage stone-free*
Eisenberger *et al* (1987)	50
Harada *et al* (1988)	51
Pode *et al.* (1988)	44
Rocco *et al* (1988)	63
Sohn *et al.* (1988)	30

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The Loss of Circadian Rhythmicity of Urinary Solute Excretion in Idiopathic Stone Formers

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Summary—Circadian rhythmicity in urinary volume and excretion of creatinine, calcium, oxalate, uric acid and phosphate was studied in 15 idiopathic stone formers and in 17 control subjects who were age-matched, related adult males, living in the same house and engaged in similar occupations to those of the stone patients, but who had no clinically obvious stone disease. Three-hourly urine samples were collected and creatinine, calcium, oxalate, uric acid and inorganic phosphate were estimated. The time series of data were analysed by cosinor rhythmometry. Circadian rhythmicity has been described in urinary volume and urinary excretion of creatinine, calcium, oxalate, uric acid and inorganic phosphate in normal subjects, but it was not detected in the stone formers. The control subjects exhibited a circadian rhythmicity only in urinary volume and creatinine excretion. Thus they occupied a position midway between healthy adults, who exhibit circadian rhythmicity in all of the above parameters, and the stone formers, who appear to have lost it altogether.

Urolithiasis represents a spectrum of disease processes with minor biochemical abnormalities at one end of the spectrum and overt, clinically manifested renal calculi, sometimes leading to renal failure, at the other. Stone recurrence was reported in as many as 80% of patients when the duration of follow-up was 15 years (Williams, 1972). Thus measures to detect subtle changes in the pattern of solute excretion at a stage before the disease is clinically manifest could be an advantage.

Circadian rhythmicity in the urinary volume and excretion of creatinine, oxalic acid, glycolic acid, phosphate, uric acid, sodium, potassium, chloride, 17-ketosteroids and 17-hydroxycorticosteroids has been reported in healthy adults (Kanabrocki *et al.*, 1983; Touitou *et al.*, 1983).

The present study was undertaken to investigate whether idiopathic stone formers and age-matched, related controls, exposed to the same climatic conditions and food habit, showed any abnormality in circadian rhythmicity in the excretion of calcium, oxalate, uric acid, phosphate, creatinine and in urinary volume.

Patients and Methods

Fifteen idiopathic stone-formers with radiologically proven renal calculi and 17 age-matched (±5 years) related adult males, living in the same house as the stone patients and engaged in similar occupations, participated in this study. None of the controls had clinical or radiological evidence of stone disease. None of the participants was on medication that could alter the chemistry of the urine or influence circadian biology. All participants were active during the day, were on a regular diet and were instructed to continue with their normal pattern of activity during the study. The study was completed within 3 months to avoid seasonal variation.

Urine samples from each subject were collected at fixed 3-hourly intervals during a 24-h span beginning at 00.00 h. The volume was recorded and samples were stored at 4°C. One aliquot was stored with a few crystals of thymol for uric acid

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determination and the other with a few drops of concentrated HCl to prevent precipitation of calcium salts. The samples were analysed for creatinine (Natelson, 1963), oxalate (Hodgkinson and Williams, 1972), calcium (Trinder, 1960), uric acid (Henry, 1967) and inorganic phosphate (Fiske and Subbarow, 1975) according to the methodology described. The urinary excretion of creatinine, oxalate, calcium, uric acid and inorganic phosphate was expressed quantitatively as mmol/3 h.

Statistical analysis

Time series of experimental data were analysed by cosinor rhymometry (Nelson *et al.*, 1979), which allows the estimation with 95% confidence limits of the parameters characterising a circadian rhythm, the period (T) equal to 24 h, since this corresponds to an average period of the subject's synchronisation; the aerophase (ø), the peak time of the cosine function used to approximate the rhythm; the amplitude (A), equal to half of the total rhythmic variability per 24 h; the mesor (M), rhythm adjusted mean, corresponds to the 24-h mean when sampling is performed at equal intervals, as in this study. Least squares method was used to find the best-fitting sine function approximating all data with this method. A rhythm was validated when its amplitude differed from zero with P 0.05. The time point location for computation was the middle of the 3-h urine collection span, *i.e.* for the 00.00 to 03.00 h span, the time point of 01.30 was used.

Single cosinor rhythmometry was performed with a SHARP scientific calculator, EL-5500 II by a programme developed by Kewal Krishan (unpublished data). The beta and gamma values obtained for each patient were then further analysed for the whole group (for stone-formers and for controls) by population mean-cosinor rhythmometry (Nelson *et al.*, 1979).

Results

The stone formers did not exhibit circadian rhythmicity in urinary volume and in excretion of creatinine, calcium, oxalate, uric acid and inorganic phosphate (Table). The control subjects exhibited a statistically significant circadian rhythm in the case of urinary volume ($P < 0.01$) with a mesor of 319 ml, an amplitude of 48.17 ml and the acrophase located at 16.03 h. These subjects also exhibited a

Table Circadian Rhythmicity in Normal Stone Formers, Subjects and Controls

Parameter	*Rhythm detection (P)*	*Mesor**	*Amplitude†*	*Acrophase‡*
Urinary volume (ml)				
Normals (4-h interval)	<0.005	219	52.5	18^{43}
Controls (3-h interval)	<0.01	319	48.17	16^{03}
Stone formers (3-h interval)	>0.05	175	—	—
Creatinine (mmol)				
Normals	<0.005	2.794	0.214	15^{30}
Controls	<0.05	0.974	0.157	16^{46}
Stone formers	>0.05	1.164	—	—
Calcium (mmol)				
Normals	<0.001	0.212	4.5	19^{48}
Controls	>0.05	0.432	—	—
Stone formers	>0.05	0.396	—	—
Oxalate (mmol)				
Normals	<0.05	0.061	0.0075	17^{16}
Controls	>0.05	0.075	—	—
Stone formers	>0.05	0.047	—	—
Uric Acid (mmol)				
Normals	<0.005	0.710	0.21	18^{44}
Controls	>0.05	0.411	—	—
Stone formers	>0.05	0.198	—	—
Inorganic phosphorus (mmol)				
Normals	<0.005	4.730	1.57	15^{47}
Controls	>0.05	2.095	—	—
Stone formers	>0.05	1.891	—	—

*Mesor: rhythm adjusted mean. †Amplitude: half of the total rhythmic variability/24 h. ‡Acrophase · peak time of cosine function.

statistically significant circadian rhythmicity in urinary creatinine excretion ($P < 0.05$), with a mesor of 0.974 mmol, an amplitude of 0.157 mmol and the acrophase located at 16.46 h (Table). No circadian rhythmicity was detected in the urinary excretion of calcium, oxalate, uric acid and inorganic phosphate in the controls.

Discussion

Epdiemiological data, particularly differences in rates of urinary stone occurrence among populations, strongly suggest that environmental factors such as diet, climate, geological factors and fluid consumption play an important aetiological role in urolithiasis (Andersen, 1973). Thus the controls, who belonged to the same ethnic group, shared the same diet and were exposed to the same climatic conditions as the stone formers, should be susceptible to urinary stone disease and may display only minor biochemical changes at first (Ahlstrand *et al.*, 1984). It is possible that eventually they may develop clinically overt disease.

Normal persons have been shown to possess a circadian rhythmicity in the excretion of creatinine, calcium, oxalate, uric acid, inorganic phosphate and urinary volume (Kanabrocki *et al.*, 1983; Touitou *et al.*, 1983). In the present study the stone formers appeared to have lost circadian rhythmicity in all of these parameters, as indeed had the age-matched, related control subjects. A long-term study, perhaps over a 10-year period, of these controls at risk of stone formation would reveal whether or not they ultimately develop clinical stone disease. If they do, then preventive measures, in the form of an increase in fluid intake and changes in dietary habit, could be adopted at a stage when they may be more effective.

In conclusion, circadian rhythmicity in urinary volume and in the urinary excretion of creatinine, calcium, oxalate, uric acid and inorganic phosphate was found to be absent in 15 idiopathic stone formers; 17 of their age-matched, male relatives who lived in the same house and shared the same diet exhibited a circadian rhythmicity only in urinary volume and creatinine excretion. Thus they occupied an intermediate position between healthy adults, who exhibited circadian rhythmicity in all of the above parameters, and the stone formers, who appeared to have lost it altogether.

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Xanthogranulomatous Pyelonephritis

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Summary—Xanthogranulomatous pyelonephritis is a rare chronic form of pyelonephritis with a clinical presentation often suggestive of a renal mass. We present 51 patients with histologically proven xanthogranulomatous pyelonephritis who were treated by nephrectomy. The results are discussed and compared with those from the literature.

Xanthogranulomatous pyelonephritis (XGP) is a rare chronic form of pyelonephritis, almost always unilateral, often associated with calculi or urinary tract obstruction, with a clinical presentation suggestive of renal mass (Anhalt *et al.*, 1972; Malek and Elder, 1978; Tolia *et al.*, 1981). More than 400 cases have been reported in the literature. Several local and systemic factors have been invoked to explain the disease. The peculiar tissue reaction could be due to either the specific effect of an organism or to a defective immune response of the host. Many micro-organisms have been isolated and Klugo *et al.* (1977) performed tests for host reactivity that were normal or temporarily altered. All authors noted that only surgery was curative and that fact, together with the high incidence of obstruction and calculi, strongly suggest local rather than systemic factors.

We have compared our patients with XGP to those described in the literature. The possibilities for early and differential diagnosis are discussed.

Patients and Methods

Fifty-one cases of histologically proven XGP (in all cases nephrectomy was done at this institution from 1970–1985) were analysed. The clinical records of all patients were studied. Associated urological and non-urological diseases were noted as well as blood count, blood chemistry, urine cultures, radiological data and surgical findings.

Results

The patients' average age was 44.8 years (range 5.5–74). The female to male ratio was almost 3.1 (female 38, male 13). All cases were unilateral, with the left kidney involved in 26 and the right in 25 cases.

The clinical signs and symptoms are presented in Table 1. The duration of symptoms ranged from 3 weeks to 27 years (mean 5.4 years). The most frequent complaints were flank pain and fever. Tender flank and mass in the renal fossa were the most common presenting signs. Lithiasis was present in most cases (82%). In nearly three-quarters of patients intravenous urography revealed a non-functioning kidney and in others stasis, dilatation, filling defects and penetration of contrast into the renal parenchyma were found.

All patients (46 were analysed) had an elevated erythrocyte sedimentation rate and in 24 (52%) it was higher than 100 after the first hour, with the highest being 152. Anaemia was found in 31 cases (67%) and leukocytosis in 32 (70%). Renal function was analysed in 46 patients by creatinine clearance and was found to be normal in 25 cases (54%); 10 patients (22%) were in the early stage of chronic renal failure; 9 (20%) were in the advanced stage and in 2 patients acute renal failure developed before nephrectomy because of pyonephrosis and urosepsis. Peritoneal dialysis was performed and renal function recovered to nearly normal levels after the operation. Hyperglycaemia was found in 8 cases (17%). Elevated bilirubin and slightly elevated aminotranspherase levels were found in 6

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Table 1 Clinical Characteristics and Radiological Findings

	No. of patients	*%*
Clinical characteristics (51 patients)		
Flank pain	32	63
Flank pain + colic	8	15
Colic	3	6
Fever	28	55
Gross haematuria	12	24
Dysuria	17	33
Weight loss	5	10
Tender flank	26	51
Positive lumbar contact	21	41
Mass in flank	20	39
Hypertension	12	24
Hepatomegaly	1	2
Radiological findings (45 patients)		
Lithiasis	37	82
Renal exclusion	34	76
Stasis and dilatation	4	9
Filling defects	1	2
Penetration of contrast	1	2

of 11 examined. The reaction of urine was acid in all cases; pyuria was found in 42 of 46 patients (91%), proteinuria in 40 (87%) and microhaematuria in 26 (57%).

Micro-organisms isolated from the urine are listed in Table 2. In 11 cases urine cultures were sterile and in 12 more than one micro-organism was isolated.

XGP was not suspected pre-operatively in any case. Tuberculosis was suspected in 5 patients, tumour in 4, polycystic disease in 1, retroperitoneal fibrosis in 1 and the remainder were treated as calculosis. Polycystic disease, retroperitoneal fibrosis and 1 case of tumour were found at operation and XGP was an associated finding. Other cases were predominantly XGP. The kidney was enlarged in 44 cases (86%) and decreased in 3 (6%). At operation two-third of the patients (34) were in the paranephric (III) stage of the disease and 17 were in the perinephric (II) stage. Sclerolipomatosis of sinus was found in 17 cases (33%).

Table 2 Urine Cultures from 45 Patients with XGP

	No of patients	*%*
E coli	22	49
Proteus mirabilis	14	31
Pseudomonas aeruginosa	9	20
Klebsiella enterobacter	4	9
Proteus rettgeri	2	4
Aerobacter aerogenes	1	2
Citrobacter	1	2
Serratia + Providentia	1	2
Strept. alpha haemolyt	1	2
Staph pyogenes	1	2
Sterile	11	25

Discussion

This study confirms that XGP predominantly affects women and adults in the fifth to seventh decades (Malek *et al.*, 1972; Gammill *et al.*, 1975; Malek and Elder, 1978; Tolia *et al.*, 1981). In 7 cases (14%) the clinical course was less than 3 months, suggesting a possible acute form of the disease. Neither the fulminant course reported by Sandler *et al.* (1980) nor the bilateral involvement reported by Rossi *et al.* (1968) was found in this series. The clinical characteristics resembled those reported by the authors of larger series (Malek and Elder, 1978; Tolia *et al.*, 1981).

The commonest organism isolated from the lower urinary tract was *Escherichia coli.* Most authors have reported *Proteus mirabilis* (Hooper *et al.*, 1962; Malek *et al.*, 1972; Malek and Elder, 1978).

In 77% of patients the diseased kidney was non-functioning, compared with 80% reported by Malek and Elder (1978).

Considering that operative treatment of pyonephrosis is the same regardless of whether XGP is present or not, the differential diagnosis is of academic interest. Early diagnosis is more important because of the inevitable loss of renal function and the appearance of XGP in children. Ballesteros *et al.* (1980) reported the possibility of pre-operative diagnosis of XGP by urinary cytology. Subramanyam *et al.* (1982) also reported the possibility of preoperative diagnosis by a combination of computed tomography and sonography.

We believe that in the case of stone disease with a disproportionately high erythrocyte sedimentation rate, especially in women, extraction of the stone should be mandatory because we have seen no case of XGP appearing after removal of the stone. The differential diagnosis with respect to tumour or tuberculosis would be of practical importance because of less extensive operative treatment and avoidance of unnecessary drugs. XGP does not seem to recur and the prognosis in patients with otherwise normal urinary tracts is excellent.

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Estimations of the S Phase Fraction *in situ* in Transitional Cell Carcinoma of the Renal Pelvis and Ureter with Bromodeoxyuridine Labelling

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Summary—This report concerns the estimation of the S phase fraction (SPF) *in situ* and its value in predicting the malignant potential of transitional cell carcinoma of the renal pelvis and ureter. Eighteen patients with transitional cell carcinoma of the renal pelvis and ureter were given a 0.5 h intravenous infusion of the thymidine analogue bromodeoxyuridine (BrdU) (500 mg) at the time of surgery to label tumour cells in the DNA synthesis phase. The tumour specimens were stained by an indirect immunoperoxidase method using anti-BrdU monoclonal antibody as the first antibody. The BrdU labelling index, S phase fraction, was determined by counting the number of bromodeoxyuridine labelled cells in the tissue sections.

All grade 1 tumours had an S phase fraction lower than 10%. The average S phase fraction for non-invasive tumour (12 cases) and invasive tumour (6 cases) were 9.7 and 20.9%, respectively. Two patients with rapid spread of ureteric tumour showed an S phase fraction of 18.4 and 22.3%. The results obtained with the S phase fraction were comparable with histological tumour grade and invasive potential. The higher S phase fraction may indicate greater biological malignancy.

We believe that determination of the S phase fraction of transitional cell carcinoma of the renal pelvis and ureter offers a new objective and quantitative assay of the biological potential of individual tumours and might have practical value in their management.

Nephroureterectomy with removal of a bladder cuff is the standard treatment for non-metastatic transitional cell carcinoma of the renal pelvis and ureter. New developments in endourological instrumentation and increasing levels of experience with these methods may provide additional opportunities to preserve renal function in patients presenting with localised disease that is not life-threatening (Johnson and Babaian, 1979; Murphy *et al.*, 1980; Smith *et al.*, 1987; Ziegelbaum *et al.*, 1987). Low grade, low stage lesions might be treated successfully by partial nephrectomy, segmental resection and endoscopic management. The use of these methods depends upon strict criteria in patient selection and a clear understanding of how best to select patients for potential conservative treatment. The controversy as to whether segmental resection or endourological management should be performed in the management of upper urinary tract transitional cell carcinoma appears to focus on the biological malignant potential of the tumour itself. We require a technique to determine the quantitative parameters that would provide the most information concerning the biological behaviour of transitional cell carcinoma of the renal pelvis and ureter.

Since tritiated thymidine became available as a marker for selective labelling of deoxyribonucleic acid (DNA) synthesis (Taylor *et al.*, 1957), autoradiographic studies of tumour cell kinetics have provided some understanding of the malignant and proliferative potential of individual tumours. However, the half-life of tritium is greater than 12 years and poses a radiation hazard both to normal tissues

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and to the environment, although the amount of radioactivity is negligible. In addition, autoradiographic studies are labour intensive, requiring several months to complete. Thus the results are of limited value in supplementing the histopathological diagnosis and planning treatment in individual patients.

Gratzner (1982) developed a monoclonal antibody directed against nuclei containing bromodeoxyuridine. Bromodeoxyuridine is one of the halopyrimidines and, like thymidine, is incorporated into cellular nuclei during DNA synthesis for mitosis (Dolbeare *et al.*, 1983). The S phase fraction may be defined by short-term exposure to bromodeoxyuridine *in vivo* or *in vitro*, provided that all S phase cells are both exposed to and able to transport and incorporate sufficent labelled precursor into DNA to give an immunocytochemical stain (Hoshino *et al.*, 1985). If these conditions are met, the bromodeoxyuridine-labelling index is equivalent to the S phase fraction (Hoshino *et al.*, 1985). Bromodeoxyuridine is neither radioactive nor myelotoxic, causes little modulation at the doses used for *in vivo* labelling studies (Hoshino *et al.*, 1985; Zang *et al.*, 1987) and enables a wide variety of human tumours to be investigated with few restrictions.

In this report we describe the results of estimating the S phase fraction of transitional cell carcinoma of the renal pelvis and ureter and compare these results with tumour grade and histological stage.

Patients and Methods

Tissue specimens from 18 patients with transitional cell carcinoma of the renal pelvis and ureter were subjected to bromodeoxyuridine labelling. All patients underwent a complete urological evaluation which included intravenous urography, chest roentgenography, nucleotide bone scan and computed tomography of the abdomen. No patient showed lymph node or distant metastasis. All histological specimens were re-examined to assure accuracy in the diagnosis of transitional cell carcinoma and to verify the tumour grade and pathological stage. Tumours were staged histologically as (1) pTa: superficial, not infiltrating the submucosa, (2) pT1: infiltrating the submucosa only, (3) pT2: invading locally into the soft tissue of the renal hilus or muscularis of the ureter and (4) pT3: invading locally through the muscularis into the parenchyma, or peripelvic or periureteric fat. Tumours were graded according to the World Health Organization system in the same fashion as bladder cancer (Mostofi *et al.*, 1973).

All patients were given a 0.5-h intravenous infusion of bromodeoxyuridine (Radibud, Takeda Drug Co. Ltd, Osaka, Japan) (500 mg) 2 to 3 h before nephroureterectomy with removal of a cuff of bladder. Informed consent was obtained from each patient. The surgical specimens were fixed with 70% ethanol, embedded in paraffin, sectioned, and stained by an indirect immunoperoxidase method using anti-bromodeoxyuridine monoclonal antibody (Fujisawa Co., Osaka) as the first antibody. The tissue sections were denatured for 1 h in 2 normal hydrochloric acid, covered with 1:30 dilution of purified anti-bromodeoxyuridine monoclonal antibody in phosphate-buffered saline, containing 0.5% Tween 20, and left at room temperature for 45 min. The slides were then incubated with a 1:200 dilution of peroxidase-conjugated anti-mouse immunoglobulin G antibody in phosphate-buffered saline for 45 min at room temperature, followed by 0.025% diaminobenzidine tetrahydrochloride with 0.003% hydrogen peroxide in tris-hydrochloride buffer for 10 to 15 min. Finally, the slides were lightly counterstained with 10% Gill 1 haematoxylin. The next portion of each section was stained with haematoxylin and eosin for routine histological examination.

About 2000 cells were counted in each of 3 to 8 microscopic fields from well-labelled areas to determine the average S-phase fraction. The fields to be counted were chosen under 40x magnification from the well labelled area, and an ocular grid at 400 × magnification was used. Malignant cells were counted consecutively in the 100-grid squares, moving from right to left and then down as in reading a page. The mitotic index was not determined. The S phase fraction was expressed as the ratio of bromodeoxyuridine-labelled cells to the total number of cells counted. When different grades were noted within the same tumor, the S phase fraction was calculated in each area. Student's *t* test was used to determine the level of statistical significance.

Results

The clinical findings and pathological diagnosis for 18 patients, and the S phase fraction of the tumours, are summarised in Table 1. Sections of alcohol-fixed surgical specimens stained with haematoxylin and eosin, and immunoperoxidase for bromodeoxyuridine, are shown in Figures 1 and 2 respectively. Immunoperoxidase staining for bromodeoxyuri-

Table 1 Clinical Data and S-phase Fraction of Patients with Transitional Cell Carcinoma of the Renal Pelvis and Ureter

Patient age (years)	*Site*	*Grade*	*Stage*	*Counted cells*	*SPF (mean ± SD)*	*Range*
EA 61	Ureter	1	pT1	2207	1.9 ± 0.6	1.2–2.7
KT 48	Ureter	1	pTa	1723	3.0 ± 2.0	2.0–4.7
NY 54	Ureter	1	pT1	1416	4.8 ± 2.3	1.7–8.5
SG 79	Ureter	1	pTa	3209	4.8 ± 0.8	3.5–5.8
OM 63	Ureter	2	pTa	1094	7.7 ± 2.9	4.2–11.5
YT 62	Ureter	1	pT1	2428	4.1 ± 0.9	2.4–5.3
		2		2691	11.0 ± 1.7	9.1–14.1
TH 65	Renal pelvis	2	pT1	2849	11.6 ± 2.2	7.6–14.9
AT 76	Renal pelvis	2	pT1	1459	11.6 ± 2.4	8.9–17.1
SS 84	Renal pelvis	2	pT1	2218	12.2 ± 2.5	8.2–14.3
SK 61	Renal pelvis	2	pT1	2353	13.5 ± 1.8	11.4–16.4
KK 50	Renal pelvis	1	pT1	1263	4.8 ± 0.9	3.8–6.9
		2		1232	14.8 ± 6.3	6.9–20.9
SS 60	Renal pelvis	3	pT2	1559	18.1 ± 3.9	14.0–24.6
KK 74	Ureter	3	pT2	1317	18.4 ± 1.8	13.6–25.7
IH 54	Ureter	3	pT2	3079	19.4 ± 3.4	13.4–24.5
OT 60	Ureter	3	pT2	1448	21.2 ± 6.3	12.6–29.3
KN 73	Ureter	2	pT2	2808	9.4 ± 1.9	6.8–12.5
		3		2320	21.9 ± 4.9	15.4–30.7
OT 73	Ureter	3	pT3	3378	22.3 ± 4.3	18.3–24.0
IT 77	Ureter	2	pT2	988	11.2 ± 3.7	7.3–16.2
		3		1416	23.3 ± 7.1	18.3–25.5

dine was confined to the nucleus and consisted of both punctate and diffuse patterns. The average S phase fraction of transitional cell carcinoma of the renal pelvis and ureter calculated from tissue sections was $12.3 \pm 6.9\%$ (mean ± standard deviation), ranging from 1.9 to 23.3%. Control sections were stained with the same technique, but the primary antibody was either omitted or replaced by an irrelevant monoclonal antibody. No nuclear staining was seen in the control sections.

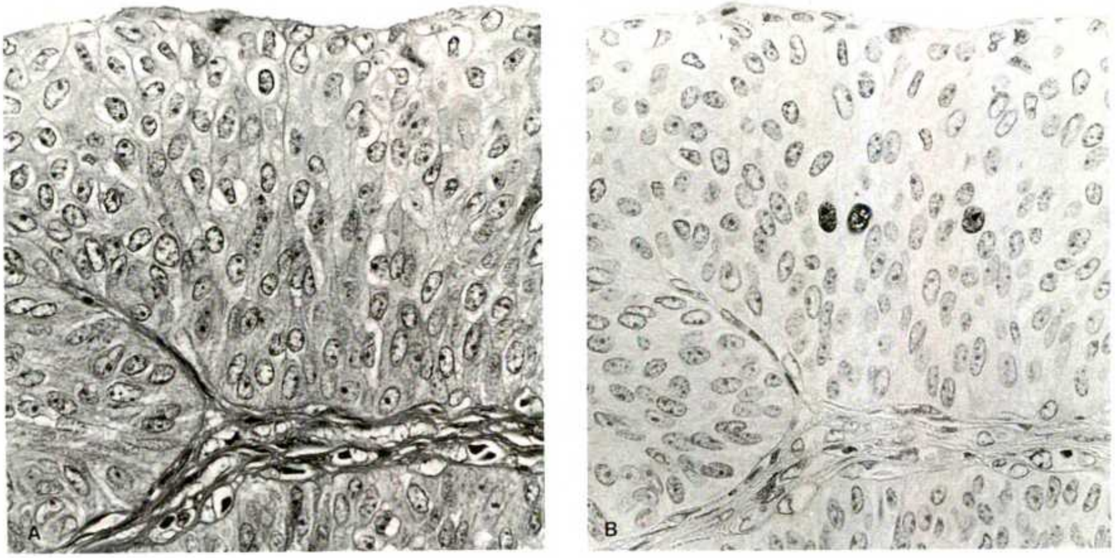

Fig. 1 Grade 1 non-invasive (pTa) transitional cell carcinoma of the ureter. (A) Alcohol-fixed tissue section. (H and E, reduced from × 100). (B) Occasional labelled nuclei are shown. (Immunoperoxidase stain for bromodeoxyuridine, counterstained with haematoxylin, reduced from × 100).

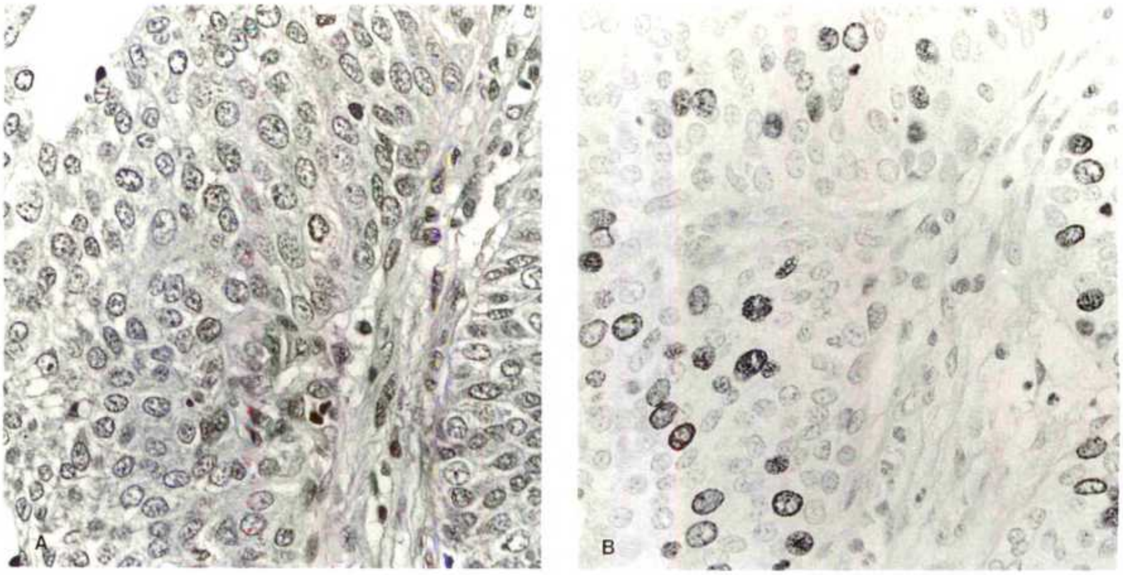

Fig. 2 Grade 3 invasive (pT2) transitional cell carcinoma of the ureter. (A) Alcohol-fixed tissue section. (H and E, reduced × 100). (B) Many labelled nuclei are shown. (Immunoperoxidase stain for bromodeoxyuridine, reduced from × 100).

Large numbers of bromodeoxyuridine positive cells were found in tumours with a high histological grade. Grade 3 tumours averaged $20.7 \pm 2.0\%$ labelling versus $11.4 \pm 2.1\%$ in grade 2 tumours, and grade 1 tumours had an S phase fraction of $3.9 \pm 1.2\%$.

In the 4 patients with varying tumour grade in different areas, the S phase fraction also showed heterogeneity corresponding with the tumour grade.

The average S phase fraction of non-infiltrative (pTa, pT1) tumours ($n = 12$, $9.7 \pm 5.3\%$) was significantly different ($p = 0.001$) from that of infiltrating (pT2, pT3) tumours invading the soft tissue of the renal pelvis or muscularis of the ureter ($n = 6$, $20.9 \pm 2.1\%$) (Table 2).

Despite total removal of ureteric tumour, 2 patients had extensive metastatic spread postoperatively and died within 1 year. In these cases the rapid spread of the tumour correlated closely with the high S phase fraction (18.4 and 22.3%) (Fig 2).

Table 2 S-phase Fraction Related to Invasion

	Non-invasive	*Invasive*
pT	pTa, pT1	pT2, pT3
No. of patients	12	6
Range	1.9–14.8	18.1–23.3
Mean*	9.7	20.9
(SD)	(5.3)	(2.1)
P value†	0.001	

*Average S-phase fraction was expressed as the per cent ratio of total BrdU-labelled cells to the total number of cells counted.
†Data were compared by using Student's *t* test.

Discussion

This study was undertaken to analyse retrospectively patients with transitional cell carcinoma of the renal pelvis and ureter and to correlate the S phase fraction *in situ*, using bromodeoxyuridine, with the malignant potential of the tumour. Our previous study on carcinoma of the bladder established that the S phase fraction correlated well with both the grade of the tumour and its invasive potential (Nemoto *et al.*, 1988). Since the urothelia of the bladder, ureter and renal pelvis are believed to share the same embryological origin, a similarity in the biological behaviour of these neoplasms would be expected.

Using our present technique, all materials stained well and the method required only 4 to 6 h to complete. The results were available with routine H and E stains for histopathological examination 5 to 6 days after biopsy. The problem inherent in renal pelvic and ureter tumours is how to obtain tissue samples for examination before extirpation, as the test cannot be performed at the time of operation. However, with continued improvements in endourological instrumentation, these approaches will probably be applied more widely in the management of patients from whom a tissue sample can be obtained using endoscopic biopsy.

Recent experience by Johnson and Babaian (1979) showed that conservative therapy has a role in the management of ureteric tumours in selected cases where the malignant potential can be determined by biopsy. Since several investigators have found a significant correlation between the depth of invasion and prognosis (Grabstald *et al.*, 1971; Mills and Vaughan, 1983), it was most important to determine from the biopsy material whether the lesion was non-invasive.

Several workers have evaluated the prognostic indicators and biological behaviour of carcinoma of the ureter and renal pelvis (Hall *et al.*, 1982; Davis *et al.*, 1987).

Our results can be expressed quantitatively to permit straightforward comparison with the histological grading of transitional cell carcinoma of the renal pelvis and ureter. On the basis of preliminary observations, low grade and non-invasive tumours appear to coincide with low SPF tumours, whereas high grade and invasive tumours may belong to a group of high SPF tumours. The SPFs obtained in this study were similar to those obtained from biopsy material from transitional cell carcinoma of the bladder (Nemoto *et al.*, 1989). The result suggests a similarity in the proliferative behaviour of neoplasms of these epithelia. Moreover, the results of this technique, used with surgical specimens from carcinoma of the renal pelvis and ureter, were comparable with the results of previous studies of patients with bladder tumours, confirming the sensitivity and reproducibility of our methods.

According to the results of the present study, the S phase fraction examination has a strong predictive value in determining the invasive potential of the tumour. More than 10% of the S phase fraction indicated an aggressive tumour with potential for invasion and this information should be helpful in deciding which patients may be treated conservatively. Complete nephroureterectomy for the patient with upper urinary tract tumour, less than 10% of S phase fraction, might be as unnecessary as total cystectomy for a superficial bladder tumour at first diagnosis.

A tumour may contain areas with different histopathological grades and heterogeneity, which causes difficulty in obtaining a representative sample. Adequate tissue sampling is, therefore, an important factor when using histopathological grade as a predictor for prognosis. The same problem will affect the results of the S phase fraction if a tumour has different S phase fraction patterns in different areas. We have already reported a possible variation of the S phase fraction within a prostatic tumour (Nemoto *et al.*, 1989). In this study, samples taken from different parts of a tumour revealed different S phase fractions, suggesting that sampling is also important when the S phase fraction is used to predict the malignant potential of transitional cell carcinoma of the renal pelvis and ureter. Moreover, the phenomenon of tumour cell heterogeneity has aroused much interest because of important implications for clinical behaviour, such as metastasising properties and response to treatment. Using S phase fraction measurements, cell clones with different S phase fraction values will be detected and thus provide information on the biology of transitional cell carcinoma in tumour heterogeneity.

The uneven distribution of labelled cells in individual tumours provides another problem in the evaluation of data obtained by these methods. Occasionally, an area which could not be stained with anti-bromodeoxyuridine monoclonal antibody surrounded a stained area where the diffusion effect could be excluded. This indicates a proliferative fraction less than 1, and implies that only a proportion of the tumour cells are cycling and contributing to growth. In experimental tumours, growth zones are not distributed randomly (Denekamp and Kallman, 1973). This has also been shown in selected human tumours (Lieb and Lisco, 1966). Proliferative kinetics, growth fraction and cell loss are dependent on vascularisation (Tannock, 1968). Transplantation experiments and *in vitro* models revealed the importance of the microenvironment to which different parts of the tumour were exposed (Broyn, 1975) and showed the dependence of the proliferative pattern on tumour geometry, nutrition and oxygenation (Tannock, 1968). In studies of *in situ* labelling of bromodeoxyuridine in human tumours, we have shown that the well labelled zones are representative of labelling indices (Nemoto *et al.*, 1988). The non-proliferative pool has important therapeutic implications since this fraction of the population is less sensitive to radiation or chemotherapy, and is probably responsible for eventual relapse following treatment. Further investigation of the distribution of S phase cells appears necessary for an evaluation of the proliferative state of transitional cell carcinoma of the renal pelvis and ureter.

This study has shown that the measurement of bromodeoxyuridine labelling index in transitional cell carcinoma of the renal pelvis and ureter may provide a new objective and quantitative assay of the biological potential of individual tumours. The results show that the S phase fraction plays a definite part in determining the invasive potential of carcinoma of the ureter and renal pelvis, and may indicate whether conservative management (partial nephrectomy, segmental ureterectomy or endoscopic management) or more extensive nephroureterectomy should be performed. Furthermore, a high SPF may be associated with a high probability of short-term relapse after initial treatment. Cell kinetics may also be useful in the selection of high-risk, node-positive patients for trials of adjuvant chemotherapy. The potential role of BrdU in the selection of those patients will be a subject of further investigation and requires long-term studies on larger numbers of patients.

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The Duplex Ureter in Burnley, Pendle and Rossendale

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Summary—Following the report of an unusually high number of patients presenting with duplex ureter in the Dorchester area, we reviewed the incidence of duplex ureter in the Burnley, Pendle and Rossendale district. Based on a review of intravenous urograms, the prevalence was found to be 3.7% (16 of 432). This confirmed the authors' clinical impression that the incidence was higher than previously quoted figures.

Duplication of the ureter is the commonest congenital abnormality of the urinary tract. Its importance lies in its association with an increased incidence of urinary tract infection and calculus formation. The true incidence of duplication is hard to assess, since radiological examinations and autopsies are performed only in certain circumstances, which vary to some degree from practice to practice. Phillips *et al.* (1987) reported a geographical focus of duplex ureter in the Dorchester area and suggested the influence of an environmental factor. We have reviewed the prevalence of duplex ureter in the district served by our hospital.

Patients and Methods

The X-ray report cards of 500 consecutive intravenous urograms requested by consultants at Burnley General Hospital were reviewed retrospectively. No form of selection was undertaken. The reports, all by consultant radiologists, were classified according to the degree of ureteric duplication and the side of duplication. Burnley General Hospital is the main hospital in the district where all 3 consultant radiologists and the district paediatric unit are based.

Results

Of the 500 X-ray reports requested, 68 were not available for review. Of the 432 reviewed, 16 (3.7%) were reported as showing ureteric duplication. Tables 1 and 2 show the age distribution of the patients, the duplications and the population. Nine of 229 patients were male and 7 of 203 were female (age range 9–84 years).

Table 1 Details of Duplications

	Left	*Right*	*Bilateral*	*Total*
Bifid pelvis	0	2	0	2
Partial	3	3	4	10
Complete	4*	0	0	4
Total	7	5	4	16

*Note that all complete duplications were left-sided.

Table 2 Age Range at Intravenous Urography

Age (years)	*No of patients*
0–9	35
10–19	31
20–29	42
30–39	63
40–49	53
50–59	65
60–69	65
70–79	57
80–89	19
90–99	1
Age not known	1

Total population of district 229,440.
Total no of intravenous urograms in 1986: 1120.

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Discussion

The true incidence of ureteric duplication is difficult to assess. However, comparison with other studies based on intravenous urograms (Table 3) suggests that Burnley, Pendle and Rossendale is a geographical focus of a higher incidence than normal, which confirmed the clinical impression of the authors. It is thought that duplication may be inherited as an autosomal dominant characteristic with incomplete penetrance.

Table 3 Ureteric Duplication Rates

Authors		*No. of patients*	%
Phillips *et al.* (1987)	Weymouth	377	2.9
	Dorchester	499	6.0
Privett *et al.* (1976)		5196	1.8
Ochsner *et al.* (1965)		10,000	0.33
Nordmark (1948)		4774	2.8

It may be possible, by comparing the incidence of ureteric duplication on a district basis, to pinpoint possible environmental or population factors. For example, it is known from analysis of all deaths in the district that 85% of those aged between 55 and 74 years who died in Burnley were born in Lancashire (Barker and Osmond, 1987). These figures would equally well support genetic or environmental influences.

It may also be possible to show that ureteric duplication is detected more often on intravenous urograms now than it was previously.

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Residual Urine Volumes in a Normal Female Population: Application of Transvaginal Ultrasound

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Summary—The volume of residual urine in a normal female population has not been studied and consequently no clear definition of its upper limit exists.

Transvaginal ultrasound has been described as a method of identifying and measuring small bladder volumes in the range 2 to 175 ml. This allows the measurement of residual urine volumes without the need for catheterisation.

Fifty-three women, who were attending for colposcopic examination agreed to take part in the study. They were deemed normal after denying specific urinary symptoms. Immediately following voiding, transvaginal sonocystography was used to measure residual urine.

Forty-five women were found to empty their bladders completely (under 2 ml residual urine). The mean residual volume was 4.8 ml. The upper limit of normal for residual urine volume (taken at the 90th centile) was 10 ml.

Several estimates for the upper limit of normal for residual urine volume in women have been suggested (Stanton *et al.*, 1983; Bergman and Bhatia, 1985; Lose *et al.*, 1987), ranging from 50 to 200 ml. The residual urine volume in a normal female population, however, has not been studied.

Transvaginal ultrasound can be applied to identifying and measuring bladder volumes (including residual urine) from 2 to 175 ml without the need for catheterisation (Haylen *et al.*, 1989a). The mean accuracy of the technique was found to be 23% in a preliminary study and 24% in a subsequent study (Haylen, 1989). Residual urine in a small proportion of normal women may exceed 175 ml.

Potential difficulties in determining a reference range for the volume of residual urine in a normal female population by urethral catheterisation include (a) ethical problems in catheterising normal women, (b) uncertainty as to the effectiveness of different types of urinary catheter in draining residual urine and (c) inability to estimate the renal input into the bladder between voiding and residual urine collection.

The use of transvaginal ultrasound, an atraumatic investigation, in women attending for vaginal examination and agreeing to take part in the study, overcame the ethical problems.

Transvaginal ultrasound also overcame the uncertainty as to whether a particular catheter completely drained the bladder. A method of calculating renal input into the bladder at different time intervals following a fluid load was described by Haylen *et al.* (1989b). Earlier experience showed that transvaginal ultrasonography could reduce the time interval between voiding and residual urine volume collection by catheterisation.

The aim of the present study was to use transvaginal ultrasound to determine residual urine volumes in a normal female population in order to establish an upper limit of normality.

Patients and Methods

Fifty-three women, median age 29 years (range 18–55), were deemed to be normal, having denied urinary incontinence or previous bladder surgery (including cystoscopy) and any of the following 5 symptoms of voiding difficulty: hesitancy, poor

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stream, need to strain to void, sense of incomplete emptying and the need to revoid immediately. All women were attending an out-patient colposcopy clinic for investigation of an abnormal cervical smear.

Each woman voided in complete privacy. Transvaginal sonocystography was performed immediately afterwards and measurements taken of any residual urine present using the formula devised by Haylen *et al.* (1989a):

Bladder volume (ml) $= 5.9 \times (\text{Height} \times \text{Depth}) - 14.6$

The time between voiding and obtaining the ultrasound image was noted, as was the amount and timing of the woman's recent oral fluid intake. Possible overestimation (accuracy) of any measured residual urine due to renal input was determined by multiplying the estimated renal input (ml/min) at the appropriate time interval following the woman's previous fluid intake by the time interval (min) between voiding and obtaining the ultrasound image (Haylen *et al.*, 1989b).

Figures 1 and 2 show residual urine volumes estimated at 4.5 and 89 ml respectively by transvaginal ultrasound.

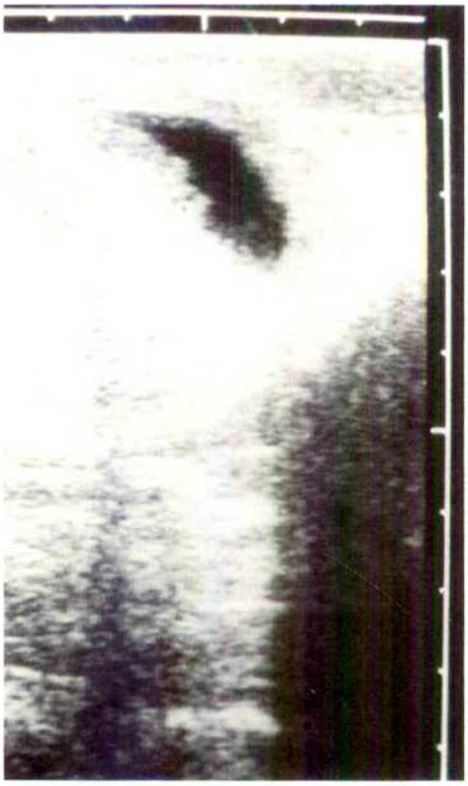

Fig. 1 Residual urine volume of 4.5 ml measured by transvaginal sonocystography.

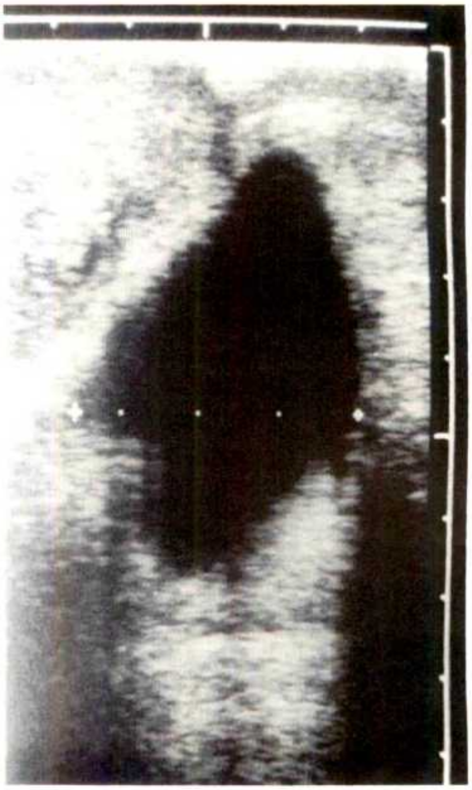

Fig. 2 Residual urine volume of 89 ml measured by transvaginal sonocystography.

Results

Figure 3 shows the incidence of residual urine volumes in a normal female population. The mean volume was 4.8 ml; 45 women (85%) had volumes which were zero or not measurable (under 2 ml) by transvaginal ultrasound. The mean time between voiding and obtaining the ultrasound image was 64 s (range 33–95). The 90th and 95th centiles for residual urine volumes in the 53 women were at bladder volumes of 9.8 and 30.3 ml.

Discussion

As reported by Hinman and Cox (1967) in their study of normal men, most normal women were found to empty their bladders completely. In only 8 of the 53 women was there any measurable residual urine (mean 4.8 ml).

Clinically, the upper limit of normal is the most

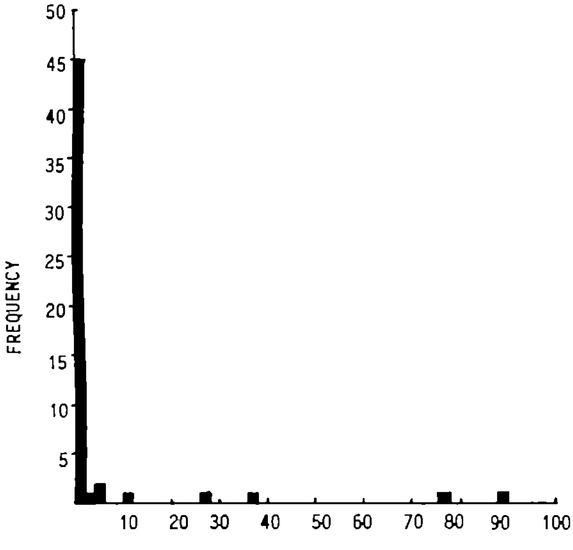

Fig. 3 Incidence of residual urine volumes in the normal female population

important aspect of the residual urine volume. If the 90th centile is used as the upper limit of normal, the relevant volume is 10 ml. Although the selection of the 90th centile is arbitrary, this limit is clearly seen in Figure 3 to be the limit higher than which only a few isolated measurements occur. This is 40 ml under the limit which has been commonly quoted (Bergman and Bhatia, 1985; Lose *et al.*, 1987). The possible overestimation of residual urine around this centile due to renal input into the bladder during the study was approximately 25%. The mean error of the technique of transvaginal ultrasound at this volume was 46% or ±4.6 ml (Haylen *et al.*, 1989a).

Transvaginal ultrasound was atraumatic and acceptable to all patients. The average time taken between voiding and measurement of residual urine (64 s) was only 24% of the average time taken for collection of residual urine by catheterisation (270 s) (Haylen *et al.*, 1989b). Any overestimation of residual urine due to renal input during the time interval between voiding and measurement would be reduced by 76%.

Whilst a suggested upper limit of residual urine in normal women has been determined by this study, no assumptions can be made regarding the level which might lead to deleterious sequelae such as urinary tract infection or upper urinary tract damage. A persistent residual urine volume of 30 ml has long been considered to have the potential for causing recurrent urinary tract infection (O'Grady and Cattell, 1966).

Transvaginal ultrasound allows a quick and accurate measurement of residual urine in women without the need for catheterisation. Compared with urethral catheterisation, transvaginal ultrasound is simpler, less traumatic and potentially more accurate.

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Verification of the Accuracy and Range of Transvaginal Ultrasound in Measuring Bladder Volumes in Women

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Summary—Transvaginal ultrasound has been presented as a technique for measuring bladder volumes in women in the range 2 to 175 ml, thus overcoming the limitations of abdominal ultrasound at these smaller, though clinically important volumes. The mean error of the technique in a preliminary study using known volumes from 10 to 175 ml was 23%.

The present study used the unknown bladder volumes of 41 women undergoing gynaecological surgery who required initial urethral catheterisation. The bladder volumes predicted by transvaginal ultrasound were compared with the volumes obtained when the bladder was emptied by urethral catheterisation. The mean accuracy rate was 24% and the optimum range was 50 to 200 ml.

The applications of this technique to the measurement of residual urine in clinical practice include the management of women with voiding difficulties and monitoring women who are either self-catheterising or who have indwelling suprapubic catheters.

In a preliminary study by Haylen *et al.* (1989), transvaginal linear array ultrasound was used to measure bladder volumes ranging from 2 to 175 ml. Known volumes were instilled into the bladder and an equation derived for predicting unknown bladder volumes from the ultrasonic measurements of 2 sagittal bladder diameters. The mean error over the range 10 to 175 ml was 23%.

In the present study the equation was applied to the measurement of unknown bladder volumes in women, in order to verify the accuracy of the technique and the range of volumes to which it can be applied.

Patients and Methods

The study group comprised 41 women who were undergoing gynaecological surgery and who required initial urethral catheterisation. All had fasted for more than 6 h before the administration of a general anaesthetic, and renal input into the bladder during the study was predictably minimal.

Immediately prior to catheterisation, transvaginal sonocystography was performed and the measurements of the 2 sagittal bladder diameters, height (H) and depth (D), as defined by Haylen *et al.* (1989), were recorded. Only bladder images confined within the limits of the ultrasound screen were included. All sonocystographic measurements were performed by the author. The bladder was then emptied using a 14 F short plastic female catheter (Pennine, UK). The ability of such a catheter to empty the bladder completely was confirmed under transvaginal ultrasonic control. Urine collection ended after the slow withdrawal of the catheter following the cessation of urine flow. This volume was measured in a 250 ml cylinder (calibration ± 1 ml checked on electronic balance).

Statistical analysis compared the bladder volumes predicted by transvaginal sonocystography using the following equation: Volume $= 5.9 \times (H \times D) - 14.6$ ml (Haylen *et al.*, 1989) with the known volumes obtained by urethral catheterisation. The mean accuracy rates of this study and the preliminary study were compared.

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Results

In Figure 1 the known bladder volumes obtained at urethral catheterisation are compared with the respective bladder volumes predicted by transvaginal sonocystography. The correlation coefficient was 0.98.

Figure 2 shows the bladder volume predicted by transvaginal sonocystography to be 207 ml; at urethral catheterisation this was measured as 224 ml (error 8%). The bladder image just reached the limits of the horizontal axis of the ultrasound screen.

The Table shows the mean errors of the transvaginal ultrasound obtained at different ranges of bladder volumes.

Discussion

There was good correlation between the bladder volumes predicted by transvaginal sonocystography and the known volumes obtained at urethral catheterisation. The accuracy of the method (mean percentage error—predicted volume from known volume) was 24%. In the range of volumes used in the preliminary study (Haylen *et al.*, 1989), the mean error of 25% obtained here was similar to the 23% obtained previously.

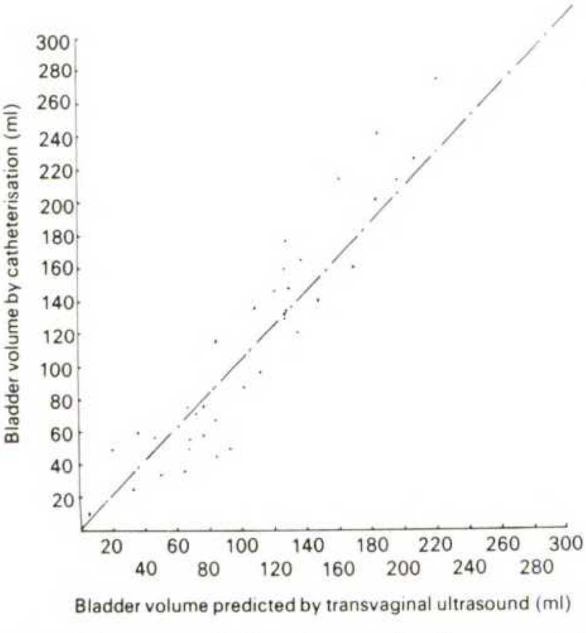

Fig. 1 The unknown bladder volumes predicted by transvaginal sonocystography compared with the known bladder volumes obtained by urethral catheterisation.

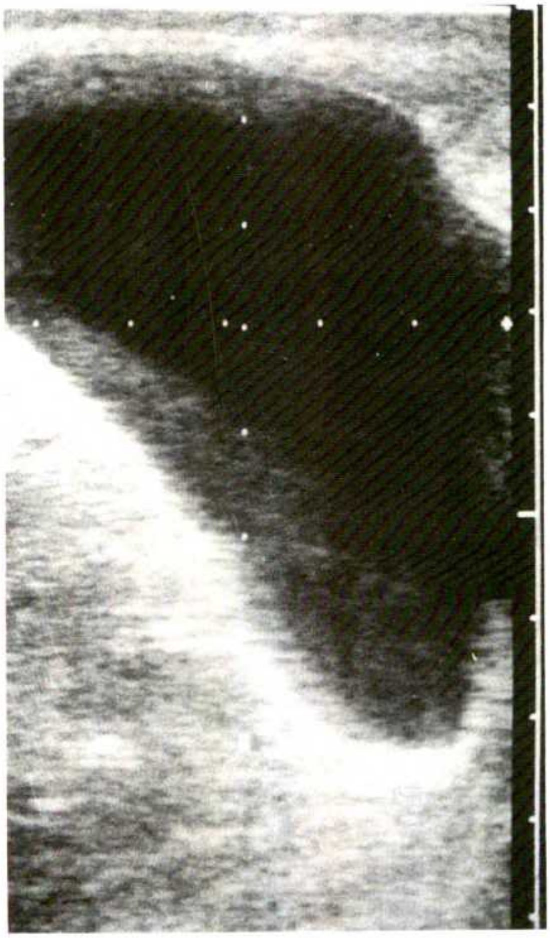

Fig. 2 Bladder volume predicted by transvaginal ultrasound to be 207 ml and measured at urethral catheterisation as 224 ml (error 8%).

The greatest inaccuracy occurred from 0 to 50 ml (56%), with the mean error at bladder volumes over 50 ml only 15%. In the preliminary study, the mean errors over the equivalent ranges were 35% (0 to 50 ml) and 16% (over 50 ml). The optimum range for this technique appears both qualitatively and quantitatively to be between 50 and 200 ml.

Residual urine volumes are generally under 200 ml. The results show that a mean level of accuracy of ±15% is possible for actual bladder volumes over 50 ml, a commonly suggested level for the upper limit of normal for the residual urine volume (Bergman and Bhatia, 1985; Lose et al., 1987). Volumes of 2 to 50 ml can still be easily visualised, though not as accurately quantified.

The errors quoted incorporate the different

Table Mean Percentage Variation (known from predicted bladder volume) over the Different Ranges of Bladder Volumes

Bladder volume (ml)	*Number*	*Mean error (%)*
0–50	9	55.7
51–100	11	15.1
101–150	11	13.9
150–200	4	16.1
over 200	6	16.9
0–200	35	25.3
All volumes	41	24.3
over 50	32	15.2

shapes and sizes of bladders during filling, a feature previously noted by others (Hackenburg *et al.*, 1983; Kiely *et al.*, 1987). The equation for transvaginal sonocystography represents the mean relationship between bladder volume and the product of the 2 sagittal bladder diameters, ignoring the differences in shape and bladder filling between individual women.

In the present series, actual bladder volumes well in excess of 200 ml (maximum 330 ml) were able to fit on the ultrasound screen and be measured with acceptable accuracy. These measurements were generally in women with anterior vaginal wall prolapse. In these cases the ultrasonic bladder image almost filled the Y (vertical) axis of the ultrasound screen, with the X (horizontal) axis proportionately slower to overfill.

Transvaginal ultrasound is a simple, quick, atraumatic and accurate method of measuring residual urine in women. The main applications in this unit have been: (i) the out-patient assessment of women with suspected or proven voiding difficulties and (ii) monitoring the residual urine volumes of women who are self-catheterising or who have an indwelling suprapubic catheter.

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Assessing the Effectiveness of Different Urinary Catheters in Emptying the Bladder: an Application of Transvaginal Ultrasound

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Summary—The effectiveness of different types of urinary catheters in completely draining the bladder has not been tested. Transvaginal ultrasound, which is able to measure bladder volumes in women from 2 to 175 ml, provides a means of measuring any fluid volume remaining in the bladder following catheter drainage.

Using transvaginal ultrasound, the post-catheterisation bladder volumes were measured in 26 female patients; 14 underwent urethral catheterisation using either a 14F short plastic female catheter or a Foley catheter of the same size (balloon not inflated); 12 had an indwelling 12F suprapubic catheter following bladder neck surgery.

The mean post-catheterisation bladder volumes after using the short plastic female and Foley catheters were less than 1 ml and 77 ml respectively. A short plastic catheter should be used in women to collect the residual urine volume by urethral catheterisation. A Foley catheter is relatively ineffective in this task.

A 12F suprapubic catheter was found to drain the bladder relatively well. The mean post-catheterisation bladder volume was 35 ml. Prior to removing a suprapubic catheter post-operatively, it is recommended that the residual urine volume (measured using the suprapubic catheter) be checked by measuring the post-catheterisation bladder volume (using either a short plastic catheter or transvaginal ultrasound).

Urinary catheters are designed to drain the bladder but how effectively they do so has not been assessed. Where a residual urine volume is being measured by any form of catheterisation, it will be underestimated by the volume of any fluid still present in the bladder following catheterisation (the post-catheterisation bladder volume).

Transvaginal ultrasound has been described as a method of identifying and measuring small bladder volumes in the range 2 to 175 ml (Haylen *et al.*, 1989a). This allows the assessment of post-catheterisation bladder volume without the need for further catheterisation.

Residual urine volumes are most commonly measured in women by urethral catheterisation (Hilton, 1987a). Two commonly used urethral catheters are a short plastic female catheter and a Foley catheter. Closed suprapubic catheterisation has become more popular following bladder neck surgery (Hilton, 1987b). One of its main advantages is that the patient's ability to void (as assessed by the measurement of residual urine drained from the suprapubic catheter) can be tested without removing the catheter and without repeated urethral catheterisation.

In the present study, transvaginal ultrasound was used to visualise and quantify bladder volumes remaining after the collection of residual urine volumes using 2 types of urethral catheter and 1 type of suprapubic catheter.

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Patients and Methods

Urethral catheters

Fourteen women attending a urodynamic clinic were included in the study. Their fluid intake was restricted in order to minimise renal contribution to bladder volume during the study to a maximum of 2.5 ml/min (Haylen *et al.*, 1989b).

Each woman emptied her bladder prior to the insertion of a 14F urethral catheter, either a latex rubber Foley (Portex, UK) or a short plastic female catheter (Pennine, UK). The balloon of the Foley catheter was not inflated. The end of collection of the residual urine occurred with cessation of flow and slow withdrawal of the catheter into the proximal urethra. This volume was noted. The catheter was then advanced into the bladder and slowly withdrawn again whilst simultaneously applying suction to the end of the catheter using a 50 ml syringe. Any further urine collected by suction and any side effects caused by the use of suction were noted.

Transvaginal cystosonography was then performed using an Aloka ultrasound camera (SSD-210 DX) and linear array probe (UST-650-5: 56 mm). The volume of any urine still present in the bladder was estimated by the following equation (Haylen *et al.*, 1989a):

$$\text{Unknown bladder volume} = 5.9 \times (H \times D) - 14.6 \text{ ml}$$

The average time from the end of the residual urine volume collection and obtaining the ultrasound image was between 1.5 and 2.0 min; 25 measurements were made (14 using the short plastic catheter, 11 using the Foley catheter). The mean post-catheterisation bladder volume was measured for each type of catheter. This volume comprised the amount collected using suction added to the volume measured by ultrasound examination.

Figure 1 shows a residual urine volume of 100 ml at the beginning of the collection using a short plastic female catheter.

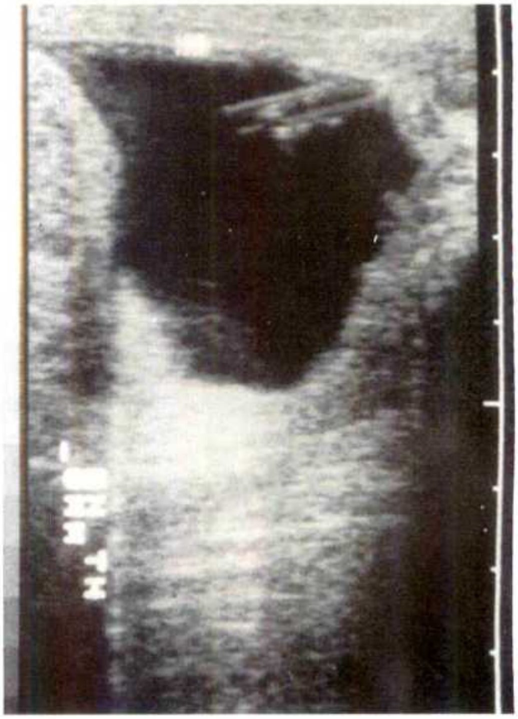

Fig. 1 Transvaginal ultrasonic image (polaroid film) of a 100 ml residual urine volume at the commencement of drainage by 14F short plastic catheter.

Suprapubic catheter

Twelve women, all of whom had undergone colposuspension for genuine stress incontinence, were studied. A 12F Cystocath (Dow-Corning, USA) was inserted at the end of the colposuspension procedure. At least 15 cm of catheter were left in the bladder for drainage.

The assessment of residual urine (using the suprapubic catheter) commenced in this unit on day 5 post-operatively. All readings were performed on day 6. To minimise renal input into the bladder during the study, the following regimen for oral fluid intake on the days of measuring the residual urine volume was adopted: 400 ml oral fluid loads were taken by the patients at 7 am, 10 am and 1 pm. At the same time the suprapubic catheters were clamped to allow the bladder to fill. Studies were then performed at least 133 min after the fluid load, when the bladder filling rate would be less than 2.5 ml/min (Haylen *et al.*, 1989b).

Immediately after the patient had voided, the suprapubic catheter was unclamped for exactly 5 min and the post-catheterisation bladder volume was measured by transvaginal ultrasound. At least 2 sets of readings were taken for each patient (30 readings in total). Figure 2 shows a typical post-catheterisation bladder volume image obtained by transvaginal ultrasound with the suprapubic catheter easily visualised.

A mean post-catheterisation bladder volume was determined for each patient. These figures were then analysed to determine a mean post-catheterisation bladder volume for the group.

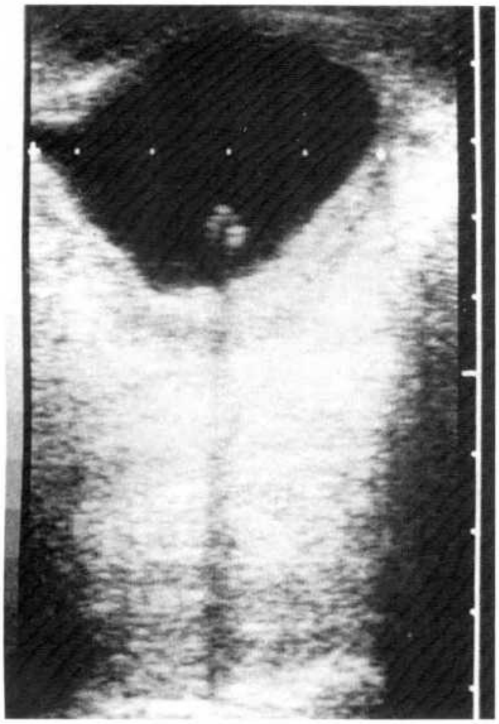

Fig. 2 Transvaginal ultrasonic image (polaroid film) of a post-catheterisation bladder volume image following unclamping for 5 min of the suprapubic catheter drain (pointing downwards in the photo, *i.e.* towards the anterior abdominal wall).

Results

Urethral catheters

The mean volumes obtained by suction and transvaginal sonocystography following residual urine collection by urethral catheterisation are listed in the Table. The sum of these 2 volumes is the post-catheterisation bladder volume for each catheter.

Suprapubic catheters

The mean post-catheterisation bladder volume for the whole group was 35 ml (range 0–97).

Discussion

The results indicate that the 14F short plastic female catheter was the most effective. The mean post-catheterisation bladder volume using the slow withdrawal technique with this catheter was less than 1 ml. There was no advantage is using suction, which tended to cause added discomfort to all patients. Evidence of blood was seen in the eye of the catheter in 29% of the patients after suction.

Significant underestimation of the residual urine volume is likely if a Foley catheter is used for urethral catheterisation, as gauged by the mean post-catheterisation bladder volume of 77 ml. Because the Foley catheter is longer and softer than the short plastic catheter, there is likely to be a corresponding increased resistance to flow. Urethral pressure appeared to exacerbate the inefficient emptying of the Foley catheter. This tendency was particularly noted in women whose urethra was narrow and more difficult to catheterise. In those same women, however, the short plastic catheter was still effective. The Foley catheter cannot be recommended for use in collecting residual urine volumes *per urethram*.

The 12F Cystocath appeared to drain the bladder quite effectively. When the decision is taken to remove a catheter post-operatively, usually when 2 consecutive suprapubic residual urine volume measurements are less than or equal to 50 ml (Bergman and Bhatia, 1985), it should be noted that an additional volume, the post-catheterisation bladder volume, may also be present. The mean of 35 ml found for this volume in the present study may not affect the patient's clinical course. However, in individual cases, this volume may be close to 100 ml. We recommend that a post-catheterisation bladder volume measurement be performed prior to final removal of the suprapubic catheter. This may be done using either a short plastic female catheter or by transvaginal ultrasound.

Certain practical observations concerning suprapubic catheterisation were evident from this study: 5 min appeared to be an adequate length of time

Table Mean Volumes Obtained by Suction and Transvaginal Sonocystography for each Catheter Type following Residual Urine Collection by Urethral Catheterisation. The Sum of these Volumes is the Post-catheterisation Bladder Volume for each Catheter

Catheter	*Mean volume obtained by suction (ml)*	*Mean volume obtained by ultrasound (ml)*	*Mean post-catheterisation bladder volume (ml)*
Disposable (n = 14)	0.7	0.1	0.8
Foley (n = 11)	44.7	32.7	77.4

for collecting residual urine by suprapubic bladder drainage (15 min were required by Mattingly *et al.* (1972)); there was very little additional urine flow after this time. No assumptions can be made regarding the effectiveness of other types of suprapubic catheter in draining the bladder within 5 min. The regimen of restricting the patient's fluid intake to certain times on the day(s) of suprapubic residual urine volume measurement proved quite practical.

The technique of transvaginal ultrasound was atraumatic and acceptable to all patients. Minor discomfort was experienced by a few patients at the limits of probe insertion, depending on the degree of angulation of the upper vagina caused by the colposuspension. Bladder neck surgery did limit expansion of the bladder in the vertical axis of the ultrasound screen, causing a tendency for the bladder image to overfill the horizontal axis of the ultrasound screen (to the left or superiorly) at lower volumes.

Transvaginal ultrasound can be applied successfully to assessing, both qualitatively and quantitatively, the effectiveness of different urinary catheters in emptying the bladder.

Acknowledgement

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Asymptomatic Bladder Neck Incompetence in Nulliparous Females

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Summary—This study investigated 29 nulliparous women using the technique of transvaginal ultrasound to assess whether their bladder necks were open or closed at rest. The patients comprised 2 groups: 4 reported occasional episodes of stress incontinence, all of whom had closed bladder necks; the remaining 25 patients were totally asymptomatic. Overall a 21% incidence of an open bladder neck was recorded. It is likely that the true incidence of open bladder necks in young nulliparous women is higher than this, since none of these patients had troublesome stress incontinence. Since women with open bladder necks are more likely to develop stress incontinence if the integrity of the distal sphincter mechanism is compromised by neural damage, antenatal recognition of this problem should provide a contraindication to traumatic vaginal delivery and may in the future reduce the incidence of symptomatic stress incontinence in the population.

Stress incontinence is a common and distressing problem in the female population. It occurs when there is a synchronous weakness of the bladder neck and distal urethral sphincter mechanisms (DSM). Although a weakness of the DSM is recognised as a sequel to pudendal nerve damage during childbirth (Snooks *et al.*, 1984, 1985), the pathogenesis of bladder neck incompetence has not yet been established. Asymptomatic bladder neck incompetence is a common urodynamic observation (Turner-Warwick and Brown, 1979), but its incidence in otherwise asymptomatic young women is at present unknown. It is of note that stress incontinence has been reported in up to 52% of nulliparous women and is a significant problem in up to 16% (Nemir and Middleton, 1954; Wolin, 1969). The intention of this study was to determine the true incidence of bladder neck incompetence in otherwise asymptomatic nulliparous women.

Patients and Methods

Nulliparous female patients entered the study with full informed consent. Preliminary ultrasound of the bladder was carried out to ensure a bladder capacity in excess of 200 ml. Transvaginal ultrasound was conducted using an Aloka SSD 256 machine with a 5 MHz linear array ultrasound probe. With the patient in the left lateral position, the probe covered with a rubber sheath (from which all air had been evacuated) was lubricated with KY jelly and inserted into the vagina (Fig. 1). This procedure was well tolerated by patients, with each investigation being rapid (5–10 min) and painless. Linear array probes of this type provide midline sagittal images analogous to lateral X-rays. The results of scans were recorded on 35 mm film which allowed subsequent analysis and review of the results by the other investigators.

Transvaginal ultrasound clearly delineates between the open and closed bladder neck (Fig. 2). The positioning of the bladder neck when in doubt could easily be demonstrated by the insertion of a small calibre Nelaton catheter, which could then be visualised on the ultrasound scan.

Review of the literature reveals that linear array ultrasound of the pelvic viscera provides accurate, reproducible results compared with conventional videocystometrography (Fellows *et al.*, 1987).

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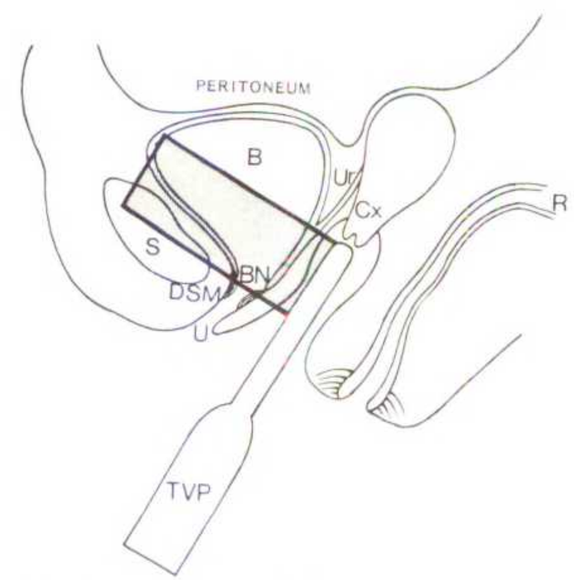

Fig. 1 Sagittal section showing transvaginal ultrasound probe (TVP) *in situ*. B = bladder. S = symphysis pubis. UR = ureter. BN = bladder neck. DSM = distal sphincter mechanism. U = urethra. Cx = cervix. R = rectum.

Results

The study group comprised 29 patients attending the Margaret Pyke Centre for routine family planning consultations. All were below the age of 40 years; 25 patients had no urinary symptoms and were nulliparous. The mean age was 26 years (range 21–36), onset of menarche 13 years (range 10–18) and the majority of patients were on an oral contraceptive agent (Table). In each case a comprehensive medical record was documented. Two patients had had laser ablation of the cervix (one having an open bladder neck), 7 had a history of urinary tract infections (4 closed, 3 open), 4 reported occasional previous episodes of stress incontinence (all had closed bladder necks). One patient had had 2 previous first trimester vaginal terminations of pregnancy plus laser ablation of the cervix (open bladder neck) and 4 patients had each had 1 first trimester vaginal termination of pregnancy (all 4 with closed bladder necks). Of the 29 patients studied, the bladder neck was found to be open on ultrasound in 6 cases, an incidence of 21%.

Table Current Contraceptive Methods

	No. of patients
Combined pill	19
Progesterone-only pill	3
Barrier method	4
Coil	2
None	1

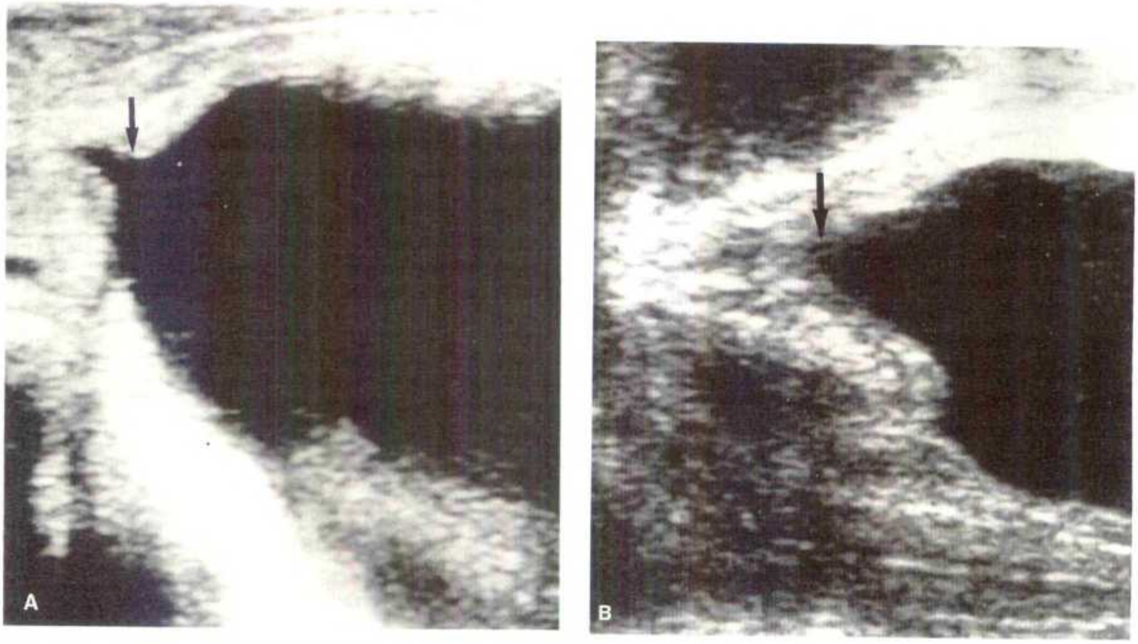

Fig. 2 Ultrasound images showing (A) open bladder neck and (B) closed bladder neck.

Discussion

It is now clearly established that linear array ultrasound of the pelvis is a useful investigative technique. Scanning via the abdomen (Bhatia *et al.*, 1987), through the perineum (Kohorn *et al.*, 1986) and via the rectum (Nishizawa *et al.*, 1982; Shapeero *et al.*, 1983; Brown *et al.*, 1985; Fellows *et al.*, 1987) provides accurate reproducible information on the anatomy of the bladder and vesicourethral junction. Transvaginal ultrasound should provide a more accurate anatomical definition of the bladder and bladder neck than any of these techniques.

Asymptomatic bladder neck opening is a common incidental finding encountered during routine urodynamic investigations (Turner-Warwick and Brown, 1979). A study using urethral pressure profilometry in 20 asymptomatic women between the ages of 25 and 74 years (mean 46 years) presenting for gynaecological surgery concluded that continence is maintained primarily by the bladder neck mechanism (Hilton and Stanton, 1983). In contrast, Versi *et al.* (1986) demonstrated that 51% of a series of continent climacteric women exhibited bladder neck incompetence, lending support to the belief that continence is largely controlled by the distal urethral sphincter mechanism.

This study has for the first time investigated young asymptomatic nulliparous women by transvaginal ultrasound and suggests a 21% prevalence of bladder neck incompetence in the absence of stress incontinence. It has been reported from epidemiological work that the incidence of symptomatic bladder neck incompetence leading to troublesome stress incontinence was up to 16% in a group of nulliparous women (Wolin, 1969). Since we excluded these groups of patients from this study, it is possible that bladder neck incompetence is a much more common occurrence than is reported here. Stress incontinence occurs only in the presence of synchronous bladder neck and distal urethral sphincter weakness. Weakness of the DSM has been shown to be associated with damage to the pudendal nerves during vaginal delivery. It is therefore likely that women with bladder neck incontinence would not only be at increased risk of stress incontinence but would also be more likely to develop this symptom if the integrity of the DSM was damaged as a consequence of childbirth. The antenatal recognition of these patients using this simple screening procedure should allow the clinician to avoid traumatic vaginal delivery and hence reduce the likelihood of their subsequently developing stress incontinence.

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The Value of Urethral Sphincter Electromyography in the Differential Diagnosis of Parkinsonism

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Summary—A series of 54 patients presenting with parkinsonism underwent clinical assessment and urethral sphincter electromyography (EMG).

After clinical assessment, 26 were thought to be suffering from probable multiple system atrophy (MSA), 15 were thought to have possible MSA and 13 were diagnosed as having probable idiopathic Parkinson's disease (IPD).

Of those with probable MSA, 16 were found to have an abnormal urethral sphincter EMG. In the group with possible MSA, only 5 patients had an abnormal EMG while in the group with probable IPD, only 1 patient had an abnormal EMG.

It was concluded that urethral sphincter electromyography provides a useful method of distinguishing between idiopathic Parkinson's disease and multiple system atrophy. It also provides a means of identifying those patients with parkinsonism whose incontinence may well be worsened, or in whom incontinence may develop following lower urinary tract surgery.

The clinical syndrome of parkinsonism has many causes, of which idiopathic Parkinson's disease (IPD) is the most common. In the brains of patients with IPD there is neuronal degeneration, confined mainly to the substantia nigra and locus ceruleus of the midbrain, and these neurones contain cytoplasmic inclusions known as Lewy bodies.

Clinically, 70% of patients with IPD have resting tremor, while all have bradykinesia and rigidity, and many may have evidence of mild autonomic abnormalities. Pyramidal and cerebellar signs are absent and they usually respond well to treatment with levodopa.

In recent years it has become clear from post mortem studies that up to 15% of patients presenting with parkinsonism may suffer, not from Parkinson's disease, but from a more widespread disorder of the nervous system known as multiple system atrophy, one variant of which is the Shy-Drager syndrome. MSA is a disease of unknown aetiology which causes degeneration with gliosis in many parts of the nervous system. Areas commonly involved are the substantia nigra, the putamen, the cerebellum, the pontine nuclei and the olives, the intermediolateral column of the spinal cord and the motor nucleus of the urethral and anal striated sphincters (Onuf's nucleus) (Konno *et al.*, 1986; Oppenheimer, 1988). The clinical presentation of the disease is variable. Extrapyramidal signs are often present (hence the confusion with IPD), but resting tremor is less common than in IPD. Pyramidal and cerebellar signs may also be present and autonomic dysfunction is almost always present, although its severity varies widely. The symptomatic response to levodopa is usually poor and the overall prognosis is worse than in IPD (Lees, 1988).

Both diseases are commonly associated with urinary symptoms but patients with multiple system atrophy have more severe incontinence and in men these problems are almost always associated with erectile impotence. Concentric needle electromyography of the striated urethral sphincter was shown to be abnormal in patients with multiple system

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Based on a Poster Demonstration at the 44th Annual Meeting of the British Association of Urological Surgeons in Buxton, June 1988

atrophy who presented with autonomic failure (Kirby *et al.*, 1986), but normal in patients with idiopathic Parkinson's disease (Fitzmaurice *et al.*, 1986). The aim of the present study was to assess the value of sphincter EMG in the differential diagnosis of patients with parkinsonism.

Patients and Methods

Fifty-four patients presenting with parkinsonism were assessed clinically and followed up. On the basis of the clinical findings the patients were divided into 3 groups: (a) probable multiple system atrophy, (b) possible multiple system atrophy, and (c) probable idiopathic Parkinson's disease.

A diagnosis of probable multiple system atrophy was made in those patients with atypical parkinsonism who had a poor or absent response to levodopa with symptomatic autonomic failure and/or pyramidal or cerebellar signs. A diagnosis of possible multiple system atrophy was made in those patients with atypical parkinsonism who had a poor or absent response to levodopa, with or without asymptomatic autonomic abnormalities. A diagnosis of probable idiopathic Parkinson's disease was made in patients with classical levodopa-responsive pure parkinsonism, regardless of autonomic symptoms.

All patients underwent urethral sphincter EMG. A concentric needle electrode was inserted into the urethral sphincter and motor unit potentials were recorded and displayed using a trigger and time delay (Fowler *et al.*, 1984); 10 individual motor units were captured and the duration of each motor unit was measured. From these measurements a mean duration was calculated for each patient.

Results

Clinical diagnosis

A diagnosis of probable multiple system atrophy was made in 26 patients (mean age 58.6 years, range 40–73); 15 had a diagnosis of possible MSA (mean age 64.9 years, range 46–73) and 13 had a diagnosis of probable IPD (mean age 65.5 years, range 54–76).

Sphincter EMG

Control data from our laboratory showed that the average motor unit duration in normal subjects was 5.82 ms (SD = 2.34). This gives a normal maximum duration of 10.5 ms (mean + 2 SD).

For each patient with a diagnosis of probable MSA or IPD, the mean duration of all of their motor units was plotted against the percentage of motor units with a duration greater than 10.5 ms (Fig.). It can be seen that the patients with MSA tended to have a greater mean duration and a greater number of abnormal motor units.

The diagnostic value of this test as a means of distinguishing patients with multiple system atrophy from those with Parkinson's disease will depend on the "cut-off" levels. If a mean duration greater than 6.5 ms and 20% or more abnormal motor units are chosen as these levels, the sensitivity of the test is 0.62 and the specificity is 0.92, assuming that the clinical diagnosis correctly reflects the pathological diagnosis.

By these criteria, 5 of 15 patients with a clinical diagnosis of possible MSA also had an abnormal urethral sphincter EMG.

Two patients with a clinical diagnosis of probable MSA have since died and this diagnosis was confirmed at post mortem. One patient had an abnormal sphincter EMG as defined above; in the other patient, although the mean duration was within the normal range, 20% of the motor units were abnormally prolonged.

Discussion

The results of these studies confirm that an abnormal urethral sphincter EMG in a patient with parkinsonism is highly suggestive of multiple system atrophy, but a normal result does not exclude the diagnosis. This abnormality of the EMG recordings is also found in the anal sphincter (Sung *et al.*, 1978) and is the result of a progressive cell loss in the motor nuclei of the striated sphincters, which are found in the S2–S4 segments of the spinal cord (Konno *et al.*, 1986). This cell loss results in the electromyographic changes of denervation and reinnervation. As a result, motor units are abnormally polyphasic and of prolonged duration.

The diagnosis of multiple system atrophy is of importance in several respects. First, the prognosis in this condition is worse than in idiopathic Parkinson's disease (Lees, 1988). Second, treatment with levodopa is likely to be less effective. Finally, and most importantly for the urologist, transurethral surgery should probaby be avoided, because removal of the proximal continence mechanism will leave the patient dependent on the distal sphincter which is demonstrably neuropathic. Although it has yet to be shown that patients with evidence of denervation of the urethral sphincter suffer urinary leakage after transurethral surgery, this seems likely to be the case.

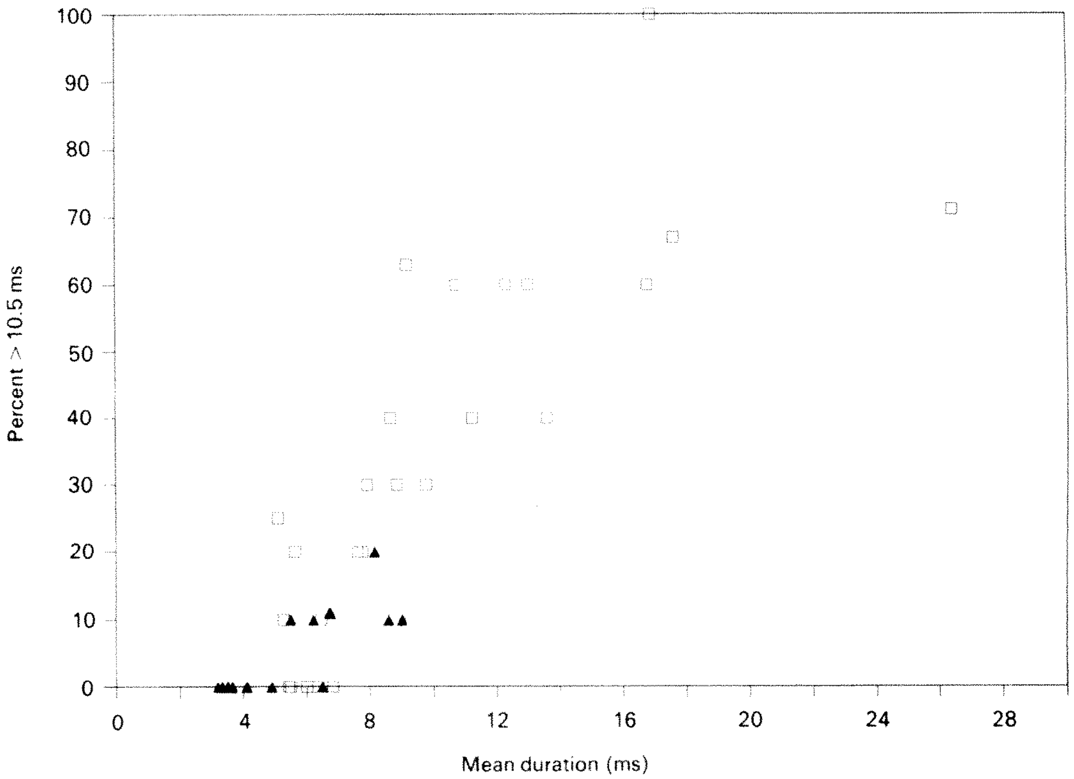

Fig. EMG urethral sphincter. Motor unit analysis. □ Probable MSA. ▲ IPD.

If EMG facilities are not available, clinical features such as pyramidal or cerebellar signs, impotence, marked postural hypotension, marked urinary incontinence and, above all, a poor response to levodopa, should alert the urologist to the possibility of a diagnosis of multiple system atrophy. In those patients transurethral surgery should be avoided.

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Stop-flow Measurement of Detrusor Contractility in Bladder Outflow Obstruction

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Summary—Detrusor contractility was evaluated by measuring the increase in isometric pressure during a stop test in 25 men with benign prostatic hyperplasia. Before transurethral prostatic resection (TUR), a low pressure increase ($\triangle P_{det\ iso}$) was associated with a large volume of residual urine. After TUR both the speed and the amplitude of isometric detrusor contractions during the stop test increased. A pre-operative low detrusor pressure increase was correlated with a great improvement in flow rate after TUR. The value of the stop-flow test was limited, however, since improvement in other urodynamic parameters could not be predicted.

The main symptoms of benign prostatic hyperplasia (BPH) are often irritative, with frequency, urgency and nocturia. Obstructive symptoms—weak urinary stream, hesitancy and intermittent voiding with straining—may also be prominent. Cystometric studies have shown a high incidence of hyperreflexia and low bladder compliance in patients with irritative symptoms (Andersen, 1982; Abrams and Schäfer, 1984). The reason why some patients with infravesical obstruction develop detrusor decompensation and a large residual urinary volume is not known, but it has been suggested that a slow depolarisation of the overstretched muscle fibres is the cause (Abrams and Schäfer, 1984). It is not clear if a large residual volume simply represents a later stage of prostatic hyperplasia, or if other underlying abnormalities in the detrusor muscle are the cause (Turner Warwick *et al.*, 1973; McGuire, 1984).

The clinical value of urodynamic examination in determining the grade of obstruction and the occurrence of unstable bladder contractions has been well documented. Earlier reports, however, disagree considerably as to whether the urodynamic study of detrusor contractility can identify patients at special risk of impaired recovery of detrusor function after TUR (Dorflinger *et al.*, 1986; George *et al.*, 1986; Jensen *et al.*, 1988).

The maximal detrusor pressure at sudden interruption of urinary flow (stop test) has proved to be a good measure of detrusor contractility (van Duyl *et al.*, 1978; Susset *et al.*, 1982). When the urethral sphincter contracts during a bladder contraction, there is a further rise in detrusor pressure to a level regarded as representing maximal bladder strength. Manual compression of the penile urethra can be used as an alternative to voluntary sphincter contraction (Morita *et al.*, 1985). The patient can also attempt to void against a total obstruction produced by an inflated urethral balloon catheter. The pre-opening pressure, *i.e.* the detrusor pressure just before urine leaves the meatus, is also an isometric pressure and was claimed to be useful in determining contractility (Coolsaet *et al.*, 1984).

In the present study, detrusor contractility was compared before and after TUR by determining the isometric pressure rise ($\triangle P_{det\ iso}$) during voluntary arrest of micturition (stop test). The velocity of this pressure rise in detrusor contraction was considered to express contraction speed.

Patients and Methods

Thirty-one men who were awaiting TUR were studied consecutively. The indications for TUR

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were established after clinical evaluation of symptoms, on the basis of previous retention and infection as well as cystoscopic and urographic findings without urodynamic data. Their mean age was 69 years (range 55–85). Six were examined 2 to 3 weeks after the first episode of acute urinary retention, but none required an indwelling catheter at the time of the study. In 2 cases the investigation was postponed until bacteriuria had been adequately treated.

Cystometry was performed after voiding. A 12 F catheter was used and isotonic saline solution (37°C) was infused at 50 ml/min; the patient was in the supine position. At desire to void, 2 subclavian polyethylene catheters, 1.45 mm wide and with 4 or 5 side holes, were introduced suprapubically under local anaesthesia. One catheter was placed in the bladder and the other in the previscal space. Both were connected to strain-gauge transducers (Statham) and the pressures were recorded on a multichannel recorder (Siemens-Elema Mingograph). The detrusor pressure was obtained by subtracting the prevesical from the intravesical pressure. Five seconds after the start of voiding the patient was asked to interrupt voiding for at least 10 s and then continue to completion. The residual urine was measured by catheterisation and thereafter the bladder was refilled to the same volume as before and the examination was repeated.

Bladder compliance (C) was calculated as the ratio of volume change to pressure at cystometry (ml/cm H_2O). Flow rate (Q), detrusor pressure at maximal flow ($P_{det}Q_{max}$) and detrusor opening pressure ($P_{det\ open}$) were determined from the mean values of the 2 voiding studies. The isometric pressure ($P_{det\ iso}$) was the detrusor pressure when the urinary flow was suddenly interrupted and the $\triangle P_{det\ iso}$ was the detrusor pressure increase at the same moment. The contraction speed was calculated from the curves by measuring the pressure increase per second from the $\triangle P_{det\ iso}$ peaks (Fig. 1). The urethral resistance factor was calculated from P_{det}/Q^2_{max}.

The investigations were repeated 6 months after TUR, with 27 of the 31 patients participating. One of the other 4 had improved and did not require TUR, 2 declined to attend and in the fourth man histological examination had revealed prostatic carcinoma. Two of the repeat studies failed technically; thus 25 men were studied before and after TUR.

Statistical analyses were made by means of Wilcoxon's test and Spearman's rank correlation coefficient with $P<0.05$ as the accepted level of significance. Methods, definitions and units conformed to standards proposed by the International Continence Society (Bates *et al.*, 1980).

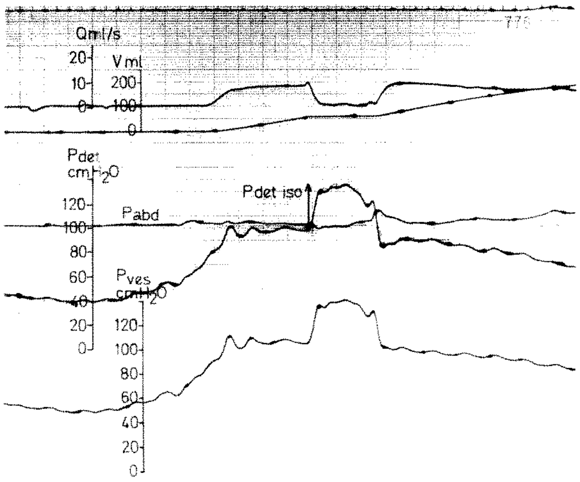

Fig. 1 Isometric contraction at micturition stop in a 65-year-old man with prostatic hyperplasia.

Results

The Table shows the mean values of the parameters before and 6 months after TUR.

Pre-operative results

Four patients had detrusor instability at cystometry (16%). Detrusor compliance was low (<20 ml/cm H_2O) in 6 men and normal (20–200 ml/cm H_2O) (Andersen, 1982) in the others. A low isometric pressure increase during the stop test was significantly ($P<0.05$) correlated with a large residual volume of urine (Fig. 2), but no correlation was found between isometric pressure increase and flow rate or detrusor compliance, or between detrusor contraction velocity and residual volume.

Post-operative results

Six months after TUR, flow rates increased and the residual volumes were smaller (Table). The detrusor pressure at maximal flow and detrusor opening pressure had both fallen in response to the reduction of outlet resistance. The maximum isometric pressure levels were also lower after TUR but the isometric pressure increase and the velocity of the isometric contraction were markedly increased.

In patients with a large residual volume and high compliance before TUR, the post-operative improvement in urinary flow rate and the decrease in

Table Functional Urodynamic Characteristics of Bladder and Urethra before and after Transurethral Resection of Prostatic Hyperplasia (means ± SD)

	Before TUR	*After TUR*	*P*
Detrusor compliance (ml/cm H_2O)	36 ± 34	40 ± 34	n.s.
Bladder capacity (ml)	461 ± 167	461 ± 118	n.s.
Flow rate (Q) (ml)	8 ± 3	21 ± 9	<0.001
Detrusor opening pressure ($P_{det\ open}$) (cm H_2O)	87 ± 28	42 ± 23	<0.001
Detrusor pressure at maximal flow ($P_{det}Q_{max}$) (cm H_2O)	106 ± 33	62 ± 23	<0.001
Total isometric pressure ($P_{det\ iso}$)	121 ± 33	84 ± 29	<0.001
Isometric pressure increase ($\triangle P_{det\ iso}$) (cm H_2O)	17 ± 9	23 ± 10	<0.01
Detrusor contraction velocity (cm H_2O/s)	8.9 ± 6.8	13.3 ± 7.3	<0.001
Urethral resistance (cm H_2O/ml/s)	3.1 ± 3.4	0.2 ± 0.3	<0.001
Residual urine (ml)	168 ± 131	45 ± 56	<0.001

residual urine were as good as in those with normal pre-operative values for residual urine and compliance. A low isometric pressure increase during the stop test before TUR was associated significantly ($P < 0.05$) with enhanced improvement of flow rate post-operatively (Fig. 3). There was no correlation between pre-operative detrusor opening pressure or contraction velocity during the stop test and post-operative improvement in flow rate or bladder emptying.

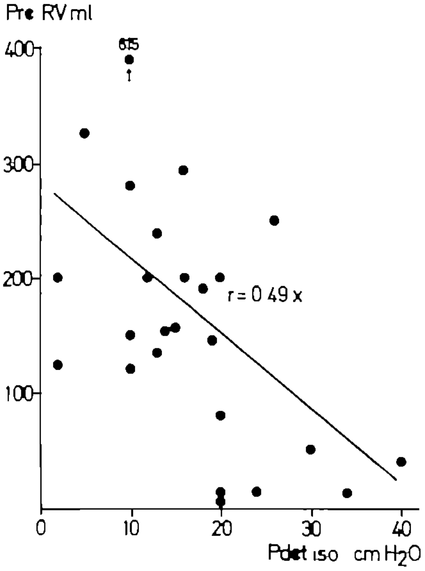

Fig. 2 Correlation between isometric pressure increase ($\triangle P_{det\ iso}$) at interrupted voiding and residual volume before TUR ($P < 0.05$)

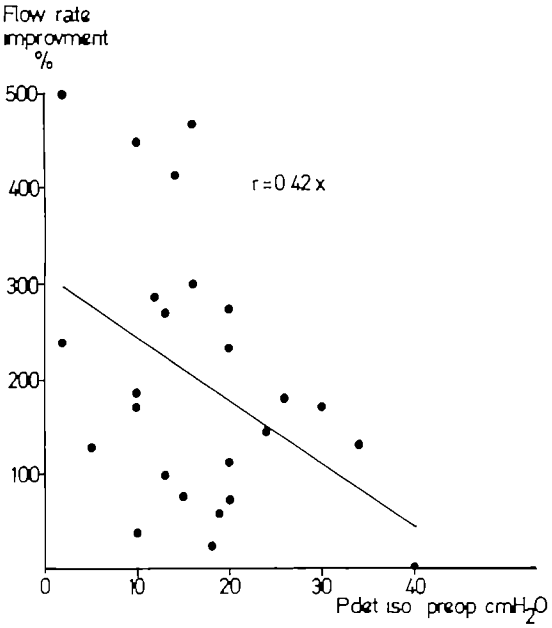

Fig. 3 Correlation between pre-operative isometric pressure increase ($\triangle P_{det\ iso}$) at interrupted voiding and improvement of urinary flow rate after TUR ($P < 0.05$)

Discussion

This study indicated that post-operative recovery of detrusor function, expressed as low contraction pressure and slow contraction velocity during the stop test before operation, was as good in men with poor detrusor contractility as in those with good contractility pre-operatively.

Isometric pressure can be readily determined during routine voiding cystometry. Its reliability and reproducibility have been questioned, however. Some of the differences in results may have been due to different recording techniques. Van Mastrigt and Griffiths (1986) recorded the isometric pressure before the start of urination, *i.e.* the detrusor opening pressure, and calculated a hypothetical maximal flow rate from the change in the bladder's spherical circumference, but found neither of these parameters to be ideal. The stop test has been criticised because it may not reflect physiologically important events. During voluntary interruption of micturition, especially if delay occurs, there is a risk that neurogenic inhibition of detrusor contraction will result in a reduced pressure rise (Abrams and Schäfer, 1984; Morita *et al.*, 1985). In studying the changes in detrusor contractility after TUR, the isometric pressure rise at arrested voiding seems preferable to the detrusor opening pressure as used by Griffiths (1977) and to the total detrusor pressure at isometric contraction recommended by Millard (1984), both of which should normally fall when the obstruction is relieved. In an extensive examination of tests which would predict the outcome of surgery for BPH, Jensen *et al.* (1988) also assessed total isometric contraction pressure and found no correlation with the patient's perception of operative success.

Significant variations in the amplitude of isometric contractions have been found with different bladder volumes. The $\triangle P_{\text{det iso}}$ was reported to be greater with a full bladder than with lower bladder volumes (Constantinou *et al.*, 1984). Other authors, however, found no such differences (Susset *et al.*, 1982). In the present study, voiding was interrupted after a constant time from the start of voiding and thus the bladder volume could not have differed much between the 2 voidings. Differences in age are reported to be unimportant in this measurement (Griffiths, 1977).

In earlier studies with stop tests in patients with prostatic enlargement, the bladder strength was found to be normal or slightly higher than in normal men, but the bladder speed was slower (Griffiths, 1977; Millard, 1984). In the present study, however, prostatic hyperplasia was associated with both reduced contractile strength ($P_{\text{det iso}}$) and low velocity of muscle contraction. Differing methods of determining the contraction velocity may explain these discrepancies. Griffiths (1977) calculated bladder speed from the maximal flow rate; in the present study, the time for the isometric pressure to reach its peak was measured directly from the curves. Marked improvement in both bladder speed and bladder strength was found after TUR.

The ability of the bladder to empty after TUR was not found to differ in men with or in those without a large volume of residual urine preoperatively, which may seem surprising and contradictory to clinical experience. For patients with chronic urinary retention and a residual volume exceeding 300 ml, Abrams *et al.* (1978) found the outcome of surgery to be poor if there was low filling pressure at cystometry. Only 2 patients in the present series had a residual volume >300 ml. Some heterogeneity in patient groups from different centres is unavoidable because of variations in the duration of obstructive symptoms before operation, different amplitudes in seeking medical advice for what are mostly insidious symptoms, and varying waiting times for TUR. This may explain the discrepancy in results. Coolsaet (1980) found that the risk of urinary retention after urethropexy in women with low pre-operatively $P_{\text{det iso}}$ was increased, but the present study indicated that patients with prostatic hyperplasia and low $\triangle P_{\text{det iso}}$ had no increased risk of persistent retention. Whether such findings also apply to men with protracted bladder decompensation is doubtful.

In the present study, TUR was followed by a marked increase in both contraction speed and in detrusor contraction during the stop test ($P_{\text{det iso}}$). The fact that patients with low pre-operative isometric contractility achieved a good improvement in flow rate after TUR may indicate that urethral resistance factors are more important in flow rate than detrusor myogenic properties. Since there was no correlation, however, between isometric pressure before operation and bladder function, other than flow rate after TUR, the stop test is probably of minor clinical importance in the assessment of men before TUR.

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The Neurogenic Overactive Bladder. Classification Based on Urodynamics

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Summary—The aetiology and pathogenesis of bladder overactivity are very variable and the classification is rather crude. By careful interpretation of clinical findings and urodynamic assessments, refinement of the diagnosis is possible. From a therapeutic and prognostic stand-point, it is of interest to distinguish between "idiopathic detrusor instability" and the "uninhibited overactive bladder". Based on neurological investigation and cystometric recordings, including the ice water test, characteristics of the 2 entities are described.

Bladder overactivity has had several designations, almost indistinguishable from one another and including detrusor dyssynergia, uninhibited bladder, spastic bladder, hyperactive detrusor, systolic bladder, unstable bladder and detrusor instability. In some instances, overactive states have been designated hypertonic or low compliant, although these terms refer to the physical properties of the bladder wall. The standardisation committee of the International Continence Society has proposed that conceptual and undefined terms should be avoided. They have suggested 2 designations: (1) "the unstable detrusor, which is shown objectively to contract, spontaneously or on provocation, during the filling phase while the patient is attempting to inhibit micturition. The unstable detrusor may be asymptomatic and its presence does not necessarily imply a neurological disorder", and (2) "detrusor hyperreflexia, which is an overactivity due to disturbance of the nervous control mechanisms. Whether the unstable detrusor is synonymous with detrusor hyperreflexia is unknown at present. Until this controversy is resolved, detrusor hyperreflexia should be confirmed by objective evidence of a neurological disorder" (Bates *et al.*, 1981).

The ICS classification, although simple, is still ambiguous and rather crude. It is founded solely on the identification, or lack of identification, of a neurogenic lesion. It must be remembered that our methods for defining discrete neurogenic lesions are limited. We would suggest a subdivision of overactive bladder states, based on cystometry and clinical evaluation.

Idiopathic detrusor instability is characterised by urgency of micturition and/or urge incontinence, normal or increased bladder sensation, phasic detrusor contractions occurring spontaneously during bladder filling or provoked by rapid filling of the bladder (Fig. 1), coughing, jumping, heel-bouncing or other external mechanical stimuli associated with increase of the intra-abdominal pressure. Voiding is co-ordinated, Bors' test (Bors and Comarr, 1971) is negative and there are no focal neurological signs. It should be remembered that asymptomatic phasic detrusor contractions may occcasionally appear in the cystometrogram

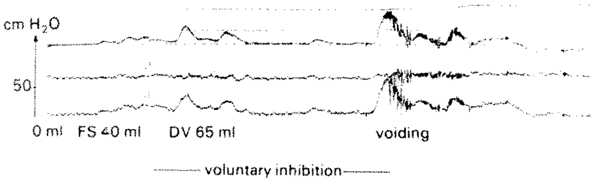

Fig. 1 Cystometric recording of patient with idiopathic detrusor instability. Phasic detrusor contractions elicited at a low filling volume, cystometric bladder capacity decreased, patient able to inhibit micturition voluntarily.

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but they seem to have limited relevance in the absence of other symptoms.

Secondary detrusor instability can be ascribed to infravesical obstruction, urethral pathology or any process involving the sensory innervation of the lower urinary tract and presents with signs and symptoms that are very similar to those of idiopathic detrusor instability. Assignment to this subgroup is based on the identification of local lower urinary tract pathology. Owing to the present lack of precise methods, it is sometimes difficult to separate this condition from idiopathic detrusor instability. In the present study, standard methods were used to exclude patients with secondary detrusor instability and it will not be discussed further.

Detrusor hyperreflexia in spinal upper motor neurone lesion, which is characterised by impairment of voluntary command of micturition, impairment or loss of bladder sensations, detrusor contraction on external mechanical stimulation, sometimes unco-ordinated micturition due to detrusor-sphincter dyssynergia, a positive Bors' ice water test and neurological deficits corresponding to the site and extent of the spinal lesion. The symptomatology and characteristics of this entity will not be further discussed in the communication, since the syndrome is well defined.

Uninhibited overactive bladder. This can be regarded as a specific entity, characterised by loss of voluntary control of micturition and impairment of bladder sensation. The first sensation of filling is experienced at a normal or lowered volume and is almost immediately followed by involuntary micturition. The patient does not experience a desire to void until he is already voiding with a sustained detrusor contraction (Fig. 2). Micturition is co-ordinated (Blaivas, 1982). External mechanical stimulation does not usually influence the detrusor. Repeated examinations may reveal that micturition is elicited at a rather fixed intravesical volume. Typically, Bors' ice-water test is positive. The uninhibited overactive bladder is present in the neurogenic bladder dysfunction following cerebral infarction, haemorrhage or tumour and is prevalent in geriatric patients (Sogbein and Said, 1982). It may also appear without obvious neurological disease. The dysfunction is resistant to therapy.

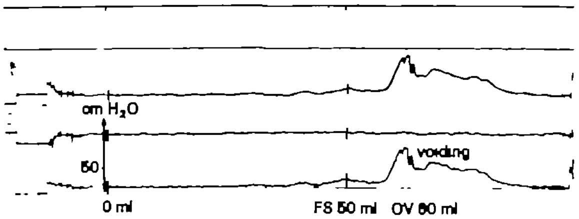

Fig. 2 cystometric recording of patient with uninhibited overactive bladder Initial phase of bladder filling normal Decrease in cystometric bladder capacity Involuntary initiation of micturition reflex, patient perceives desire to void only when micturition contraction is maximal and is unable to inhibit micturition voluntarily

This study was performed to make a comprehensive neurological evaluation of patients with urodynamic features typical of subgroups of overactive bladder. Sixteen patients had an uninhibited overactive bladder (UOB) and 10 had idiopathic detrusor instability (IDI); 9 patients with low pressure hydrocephalus were studied as a reference group.

Patients and Methods

A prerequisite of inclusion was a characteristic urodynamic presentation. Moreover, the patients presented long-standing urinary frequency and/or urge incontinence evaluated from the history and micturition charts. Lower urinary tract inflammatory disorders and infravesical obstruction were excluded by urethrocystoscopy, repeated culture of urine and urodynamic investigations. In a consecutive series, 16 patients (7 women and 9 men) were assigned to the UOB group (age range 23–83 years, mean 59) and 10 patients (7 women and 3 men) assigned to the IDI group (age range 23–66 years, mean 51). Nine patients from the Department of Neurology (2 woman and 7 men, age range 60–75 years, mean 67) with hydrocephalus were selected for urodynamic studies and examined before any therapeutic measures were taken.

Urodynamic methods

Determination of the micturition flow rate and residual urine volume, cystometry and Bors' ice water test were performed in all patients. The flow rate was measured with a 21 C 10 mictiometer and 21 K 02 uroflow transducer (Disa Electronic, Denmark). The residual urine volume was obtained by means of an 8 F baby-feeding tube introduced through the urethra immediately after voiding in privacy. Cystometry was performed as follows: two 8 F plastic catheters were introduced through the urethra into the bladder. Isotonic saline at room temperature was infused at a rate of 40 ml/min through one of the catheters. The second catheter was connected via a pressure transducer (EMT 34, Siemens Elema, Sweden) and amplifier to an ink recorder (Mingograph 81, Siemens Elema), by means of which a continuous recording of the bladder pressure was obtained. The rectal pressure was recorded simultaneously with a balloon catheter and electrically subtracted from the intravesical pressure. In patients with normal cystometry in the supine position, repeat cystometry was performed in the seated or standing position, with coughing at regular intervals during filling of the bladder. The pressure slope during filling, the presence of abortive detrusor contractions, the appearance of the sustained micturition contraction and the volumes at first sensation and desire to void were registered.

Bors' ice water test was performed as follows: 100 ml of sterile water at 0°C were infused from a glass syringe as rapidly as possible. The bladder pressure was recorded simultaneously. A positive test implied bladder contraction (with expulsion of fluid) within 1 min.

Neurological examinations

A careful history was taken in all cases and a comprehensive routine examination performed. A CT scan was done in all but 6 patients.

Symptoms, signs, diagnoses, measures and abnormalities of the CT scan that could possibly have some significance in the development of the bladder disorder are presented in Tables 1, 2 and 3. The list includes cerebral infarction, widening of ventricles and other possible lesions of the central nervous system caused by meningo-encephalitis, electroconvulsive therapy and Parkinson's disease. Possible damage to the peripheral nerve supply of the bladder in connection with surgery to lumbar discs,

Table 1 Uninhibited Overactive Bladder

Patients (sex)	*Other symptoms, signs, diagnoses and measures*	*CT scan*	*Sensation of filling normal/abnormal*	*Infused volume at first abortive contraction (ml)*	*Voluntary control of micturition*	*Bors' test*	*Cystometric capacity (ml)*
1 IB (M)	Hemiplegia	Large cerebral infarction	Abnormal	—	No	Positive	255
2 BB (M)	Daily headache, unspecified vertigo	Widened ventricles	Abnormal	80	No	Positive	100
3 SB (M)	Memory defects	Small frontal infarction	Abnormal	50	No	Positive	50
4 AG (M)	Mb. Menière	Normal	Abnormal	—	No	Positive	180
5 FG (F)	0	Normal	Abnormal	—	No	Positive	120
6 AK (M)	Meningo-encephalitis	Normal	Abnormal	20	No	Positive	45
7 RP (F)	Hysterectomy	Normal	Abnormal	—	No	Positive	60
8 ÅS (M)	0	Not performed	Abnormal	—	No	Positive	80
9 MS (F)	Electro-convulsive therapy	Widened ventricles cortical atrophy	Abnormal	—	No	Negative	150
10 ÅS (M)	0	Normal	Abnormal	—	No	Positive	130
11 BT (F)	Depressive mode. Takes tricyclic antidepressive drug regularly	Not performed	Abnormal	—	No	Positive	120
12 RT (M)	Diabetes mellitus	Normal	Abnormal	—	No	Positive	275
13 MÖ (F)	Incipient Parkinson's disease	Normal	Abnormal	—	Able to inhibit for 30 s but not more	Positive	170
14 LJ (M)	Daily headache, unspecified vertigo	Widened ventricles	Abnormal	—	No	Positive	190
15 GR (F)	Operated thyrotoxic goitre	Normal	Abnormal	—	No	Negative	190
16 ML (F)	0	Not performed	Abnormal	—	No	Negative	350

Table 2 Idiopathic Detrusor Instability

Patients (sex)	*Other symptoms, signs, diagnoses and measures*	*CT scan*	*Sensation of filling normal/abnormal*	*Infused volume at first abortive contraction (ml)*	*Voluntary control of micturition*	*Bors' test*	*Cystometric capacity (ml)*
1 SH (M)	Upgaze palsy, unspecified vertigo attacks	Small frontal infarction	Normal	225	Yes	Negative	280
2 AH (F)	Headache of tension type, numbness in the left side of the body	Normal	Normal	—	No	Negative	600
3 BL (F)	0	Normal	Normal	310	No (dribbling)	Negative	420
4 LP (M)	Marked overweight	Widened ventricles	Abnormal	300	No (dribbling)	Negative	450
5 HF (M)	0	Not performed	Normal	175	Yes	Negative	245
6 IJ (F)	Myeloproliferative disease	Normal	Normal	190	Yes	Negative	330
7 EA (F)	Operated lumbar disc hernia	Normal	Normal	—	No	Negative	280
8 HK (F)	Operated lumbar disc hernia, operated extra-uterine pregnancies twice	Normal	Normal	85	Yes	Negative	115
9 AKÖ (F)	0	Not performed	Normal	140	Yes	Negative	285
10 AL (F)	Depressive mode, require tricyclic antidepressive drug regularly	Not performed	Normal	70	Yes	Negative	115

Table 3 Hydrocephalic Patients

Patients (sex)	*Other symptoms, signs, diagnoses and measures*	*Sensation of filling normal/abnormal*	*Infused volume at first abortive contraction (ml)*	*Voluntary command of micturition*	*Bors' test*	*Cystometric capacity (ml)*
KOJ (M)	Gait disturbances. Emotional blunting	Abnormal	—	No	Positive	60
VT (F)	Gait disturbances Memory defects	Normal	—	Yes	Positive	550
AO (F)	Memory defects. Vertigo	Abnormal	40	No	Positive	60
EO (M)	Gait disturbances Memory defects	Abnormal	—	No	Negative	710
NE (M)	Gait disturbances. Memory defects Depressive mode	Normal	—	No	Positive	220
LEE (M)	Gait disturbances Emotional blunting	Abnormal	80	No	Positive	110
ÅR (M)	Gait disturbances. Compulsive disorder	Normal	—	No	Negative	230
AJ (M)	Gait disturbances Memory defects	Abnormal	—	No	Positive	180
PE (M)	Gait disturbances	Abnormal	—	No	Positive	220

extra-uterine pregnancies and hysterectomy is also included.

Results

The urodynamic and neurological findings are listed in Tables 1, 2 and 3. The patients classified as having UOB all had a number of cystometric findings consistent with this urodynamic diagnosis (Table 1). Thus they had signs of a sensory defect presenting either as lack of first sensation or desire to void, or both, or involuntary initiation of micturition contraction before the desire to void. Bors' ice water test was positive in all but 2 cases. Only 1 patient in this series (No. 1) had gross focal neurological signs, while in the remainder a detailed neurological evaluation revealed no focal signs but unspecific symptoms were frequently noted, *e.g.* vertigo, memory defects and headache. Such symptoms were less frequent in patients with IDI (Table 2). In this group, all but 1 patient had normal bladder sensation during filling, all but 4 had voluntary control of micturition and Bors' ice-water test was consistently negative. Patients with documented hydrocephalus all had urodynamic findings similar to the UOB syndrome. All presented neurological and mental signs and symptoms like gait disturbances, memory defects and emotional blunting (Table 3).

At CT scanning, patient No. 1 (Table 1) had a large infarction after cerebral haemorrhage. Widening of the ventricular system consistent with some degree of cerebral atrophy was noted in 3 men with UOB and 1 with IDI and previously unknown small frontal infarctions were detected in 2 patients, 1 from the UOB and 1 from the IDI group (Tables 1 and 2).

Discussion

Neurogenic bladder dysfunction characterised by an overactive detrusor may have several causes: gross damage or malformation of the spinal cord or intracranial structures, discrete central nervous system lesions, *e.g.* in some cases of MS, or conditions without other focal neurological signs. An overactive detrusor may be found in connection with defective urethral closure in the female and infravesical outflow obstruction in the male (Bates, 1971; Petersen and Erichsen, 1987; Speakman *et al.*, 1987), indicating that disturbances of the sensory input may result in defective motor control of the bladder. Experimentally, phasic detrusor overactivity has been correlated to an imbalance of a positive feed-back system from vesical pelvic nerve afferents to efferents. The positive feed-back mechanism, which is tonically inhibited, is an adequate mechanism to achieve complete emptying but may go out of control and thus predispose to detrusor instability (Lindström *et al.*, 1984).

Detrusor overactivity can result from dysfunction of any part of the reflex loops between the bladder afferents to efferents and focal neurological diagnosis cannot be based on the cystometrogram alone. To use the presence of a detectable nerve lesion as a decisive criterion is, however, a simplistic method of classification. It may reduce the possibilities of identifying different aetiological and pathogenic mechanisms. A more elaborate classification can improve the identification of common pathogenic factors in separated subgroups. Subdivision into subgroups has been reported by others, *e.g.* Stephenson and Wein (1984), who divided the unstable bladder into a "congenital group", "idiopathic instability of middle age" and "degenerative instability". Our attempts at classification refers primarily to cystometric findings, since we believe that there are a few typical urodynamic features which make subdivision of overactive bladder states possible.

Cystometry has been regarded as the "reflex hammer" of the neuro-urologist (Bors and Comarr, 1971; Lapides, 1976). It is the instrument used to distinguish upper from lower motor lesions and, when combined with supplementary techniques, also makes it possible to identify subtle neurological lesions (Susset *et al.*, 1984; Blaivas *et al.*, 1985). If performed and interpreted carefully, routine cystometry can be of further use. We have demonstrated some features in the recordings of subgroups with detrusor overactivity. The UOB appears to represent a specific urodynamic entity, demonstrating a perception defect, a serious defect of the control mechanisms of vesical motor pathways and poor voluntary sphincter control. It has been shown previously that patients with cerebral damage frequently present part of, or the entire UOB symptom complex (Tsuchida *et al.*, 1983). As demonstrated in this series, small and previously unknown cerebral lesions, such as small frontal infarctions or widening of the ventricular system, will be detected in some supposedly neurologically normal patients by careful examination, including CT scanning or similar techniques. In others, the precise site of the lesion cannot be revealed with techniques currently available. Although the UOB can be correlated to damage to cerebral matter, it is not neurologically specific. It must be emphasised that the various urodynamic subgroups do not represent completely separate neurological entities but rather some typical patterns. There are doubtless borderline cases, *e.g.* patients 2 and 7 (Table 2), in whom 2 criteria differed from the general features of IDI. Two patients diagnosed as UOB (patients 15 and 16, Table 1) had a negative Bors' test but fulfilled the other criteria of UOB. It may be that the entities are separated not on quantitative (the extent of a CNS lesion) but rather on qualitative grounds (the precise site of a lesion or a local change on the receptor level). Recent clinical and experimental work suggests changes of adrenoceptor, endorphin and vasoactive intestinal polypeptide activity in bladder overactivity (Murray and Feneley, 1982; Gu *et al.*, 1983; Murray, 1983).

The sensory defect may be of crucial importance in the UOB syndrome. Since perception is decreased owing to nerve damage, the patient receives no warning and cannot control the detrusor reflex. This sequence also involves a defect of urethral control (Hindmarsh *et al.*, 1983). Some of the patients experience a desire to void only when the afferent inflow is maximal at the peak of intravesical pressure during the micturition contraction (Lindström *et al.*, 1984), but this is too late as the bladder is already emptying.

The natural course of the urodynamic abnormality IDI is that this finding is constant over long periods (Booth *et al.*, 1981). In some cases, however, IDI may progress to the more severe condition UOB. The contrary course is almost never seen. A patient with UOB may occasionally present a fluctuating course with periods of remission of symptoms and objective findings, usually coinciding with general improvement of cerebral function. The temporary improvement in bladder function in the hydrocephalic patient after decompressive lumbar puncture is another example of reversibility. In our experience, in contrast to IDI, patients with UOB respond inadequately to anticholinergic treatment. Bladder drill may improve but will not cure the condition. Conventional long-term electrical pelvic floor stimulation is usually not as effective as in IDI. However, maximum electrical stimulation has an effect in the UOB (Ohlsson *et al.*, 1989).

Subdivision of overactive bladder dysfunction gives better prognostic information. The use of Bors' ice water test as part of routine cystometry is recommended, since it provides a means of refinement in the classification of overactive bladder states. The neurophysiological explanation for the specific provocative effect of the test is probably that this "cooling reflex" uses a pathway separate from the tension receptor system (Fall *et al.*, 1987). With increasing knowledge of bladder physiology and pathophysiology and more sophisticated tests and clinical investigations, such as electrophysiological testing and NMR, continuous improvement in the classification of overactive bladder states would be possible. This seems mandatory in order to improve the selection of treatment.

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Effects of External and Direct Pudendal Nerve Maximal Electrical Stimulation in the Treatment of the Uninhibited Overactive Bladder

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Summary—Maximal electrical stimulation (MES) administered from a laboratory device designed to deliver stimulation pulses of relatively high voltages and currents was performed in 29 patients. All had suffered from bladder overactivity for several years, either idiopathic detrusor instability or an uninhibited overactive bladder, and all had failed to respond to conservative treatment.

MES was performed in female patients by means of intravaginal and intra-anal electrode carriers and in males by anal electrodes only. In some cases additional stimulation was administered by means of a single needle bipolar electrode inserted directly into the pudendal nerve. Maximal amplitude was attained after gradual increases in amplitude and the patient's adaptation to this. Stimulation was administered by the therapist but the amplitudes were determined by the patient and limited by his/her pain threshold. Alternating rectangular constant voltage pulses at a repetition rate of 10 Hz were used. Treatment consisted of 4 sessions of stimulation with intervals of 1 week between each application.

All patients showed a significant increase in functional bladder capacity and 11 reported a 30% decrease in the frequency of micturition. Two patients were unaffected by stimulation with external electrodes but responded well to direct pudendal nerve stimulation. MES seems to be an effective first-line treatment for the uninhibited overactive bladder.

Electrical stimulation is used in the restoration of urinary continence by activation of the closing musculature of the urethra and inhibition of premature bladder contractions. These effects are achieved by electrical stimulation of the pudendal nerve (Fall *et al.*, 1977a; Teage and Merill, 1977; Lindström *et al.*, 1983, 1984; Ohlsson *et al.*, 1986). External electrodes often produce excellent results (Godec and Kralj, 1976; Sotiropoulus *et al.*, 1976; Fall *et al.*, 1977c; Plevnik and Janez, 1979; Janez *et al.*, 1982; Suhel *et al.*, 1982; Plevnik *et al.*, 1986).

The nervous pathways mediating electrical stimulation have been explored in cats (Fall *et al.*, 1977a; Teage and Merill, 1977; Lindström *et al.*, 1983) and appropriate electrical parameters, which are different for bladder inhibition and urethral closure, have been determined. Alternating rectangular pulses, at a repetition rate of 10 Hz, are effective for bladder inhibition, whereas 20 to 50 Hz appears optimal for urethral closure (Erlandson *et al.*, 1977; Lindström *et al.*, 1983; Ohlsson *et al.*, 1986).

Long-term, low amplitude electrical stimulation has led to relief of symptoms and even cure in a number of trials (Caldwell *et al.*, 1968; Riddle *et al.*, 1969; Alexander *et al.*, 1970; Hopkinson *et al.*, 1972; Collins, 1972, 1974; Doyle *et al.*, 1974; Fall *et al.*, 1977b, 1986; Fall, 1984; Eriksen and Mjölneröd, 1987; Ohlsson, 1987a).

In patients suffering from an uninhibited overactive bladder—bladder hyper-reflexia caused by lesions in the CNS due to tumours, haemorrhage, infarction or unknown causes (Fall *et al.*, unpublished data)—long-term electrical stimulation has been less successful. Unfortunately, the results of other forms of treatment are also poor. Acute

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maximal electrical stimulation may be more efficient than long-term stimulation since high amplitude stimulation induces more pronounced bladder inhibition (Lindström *et al.*, 1983, 1984; Ohlsson *et al.*, 1986; Vodusek *et al.*, 1986). Maximal electrical stimulation has been reported to be successful (Plevnik *et al.*, 1979; Janez *et al.*, 1982; Suhel *et al.*, 1982; Vereecken *et al.*, 1984; Plevnik *et al.*, 1986).

The aim of the present study was to ascertain whether short-term stimulation, at a relatively high amplitude, influenced bladder overactivity in patients with an uninhibited overactive bladder (UOB) or idiopathic detrusor instability (IDI).

Patients and Methods

The study included 29 patients, 13 women and 16 men, with symptoms of urge incontinence. Their mean age was 52 years (range 15–83). All underwent clinical and urodynamic investigations, including cystoscopy, flow measurement and cystometry in the supine or standing position prior to initiation of treatment. Residual urine was determined.

Cystometry in 19 patients showed a normal pressure slope until a sustained detrusor contraction suddenly occurred, usually followed by involuntary emptying of the bladder. The Bors' ice-water test was positive, implying involuntary bladder emptying owing to bladder contraction after the instillation of 50 to 100 ml of ice water. This dysfunction was known as the uninhibited overactive bladder.

In 10 patients repetitive detrusor contractions occurred during bladder filling and the Bors' ice-water test was negative. This cystometric pattern was consistent with idiopathic detrusor instability.

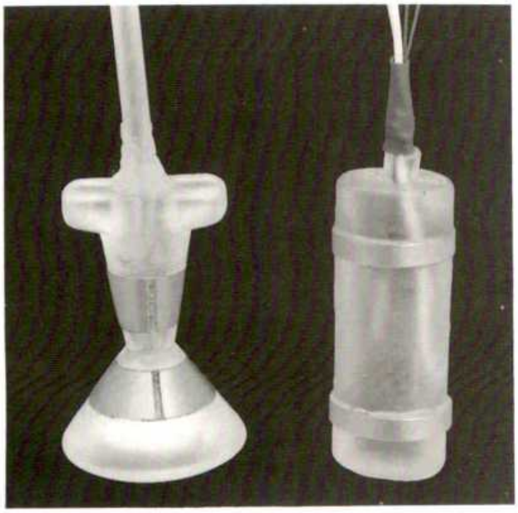

Fig. 1 Anal (left) and vaginal (right) electrode carriers.

Specially designed electrode carriers were applied. Each female patient was treated by means of one vaginal and one anal electrode carrier, while each male patient was provided with the anal electrode carrier (Fig. 1). The vaginal electrode carrier had an oval cross-section of radii 11 and 9 mm and length 55 mm. The width of the electrodes was 4 mm and the distance between them 27 mm. The anal electrodes were attached to a plug whose maximum diameter was 28 mm. The segment between the electrodes, for location in the anal sphincter, had a minimum diameter of 9 mm. The distance between the electrodes and the electrode widths were 8 mm and 10 mm respectively.

In all stimulations the vaginal and anal electrodes were supplied from constant voltage stimulators, allowing stimulation at relatively high voltage and corresponding current amplitudes.

Patients who were marginally affected by external stimulation had additional sessions of electrical stimulation by means of a bipolar needle electrode inserted transperineally to the pudendal nerve (Janez *et al.*, 1982) and guided by rectal palpation. Appropriate location of the needle was checked during stimulation. The hallmark of proper positioning was visible and palpable unilateral contractions of the pelvic floor in synchrony with stimulation.

For each set of electrodes the voltage amplitude was increased gradually in order to accustom the patient to stimulation. When he/she could tolerate no further increases, stimulation was continued at this level for 20 min. Currents and voltages were monitored on an oscilloscope (Hewlett-Packard 1200 A).

Rectangular alternating pulses at a repetition rate of 10 Hz and pulse duration 1.0 ms were administered.

The current amplitudes varied widely between patients, according to their sensory threshold (Ohlsson, 1987b) but were relatively constant for each patient during the 4 stimulation sessions. The end-value of the current pulses arising from constant voltage pulses of different durations ranged from 5 to 120 mA for vaginal and from 2 to 120 mA for anal stimulation. Corresponding constant voltage amplitudes were 5 to 22 V and 3 to 15 V respectively. For direct pudendal nerve stiumulation, current amplitudes between 0.5 and 5 mA and voltages between 5 and 22 V were used.

Each patient was asked to record micturition frequency, voided volumes and incidental leakage of urine during 24-h periods before and after treatment. Some elderly patients failed to complete the chart and since only the records of micturition frequency were available, it was not possible to use the rate of incidental leakage in assessing results.

Urodynamic investigations were repeated 1 month after the last stimulation session and changes in micturition frequency, functional bladder capacity and ability to inhibit bladder contractions were noted. The Bors' ice-water test was repeated.

Statistical calculations were made using a parametric Student's *t* test and a non-parametric Wilcoxon matched pairs test. In the former, attention was paid to the logarithm of the ratio of bladder capacities and micturition frequencies, as measured before and after treatment. The parametric test was performed on the assumption that the ratios of post- and pre-stimulation parameters were logarithmically normally distributed (Holm, 1982). For the non-parametric test the distribution of the ratios can be arbitrary (Breiman, 1973; Bailey, 1976; Holm, 1982).

Results

Nineteen patients had an uninhibited overactive bladder. The urodynamic parameters and micturition charts recorded before and after treatment were compared. Changes in the urodynamic parameters are shown in Figure 2.

MES by means of external electrodes increased the bladder capacity in 13 patients (25–440 ml before treatment and 40–500 ml after treatment). The increase ranged from 9.1 to 100% (average 49%), corresponding to rises in volume from 10 to 180 ml.

Ten patients noted a decrease in frequency of micturition and in the remaining 9 patients it was unchanged. Frequency ranged from 6 to 36 micturitions both before and after treatment. The reduction ranged from 5 to 63% (mean 33%).

After treatment, 3 patients regained the ability to inhibit bladder contractions (1, 8 and 10 in Fig. 2). The desire to void occurred at considerably higher volumes in 2 of these patients, who also showed a change in the result of the Bors' ice-water test. Four patients were able to inhibit their bladder contractions even before treatment and 2 of them (15 and 18) reported a significant decrease in frequency and an increase in bladder capacity following treatment. In 1 male patient (8) all parameters improved and he experienced a dramatic recovery.

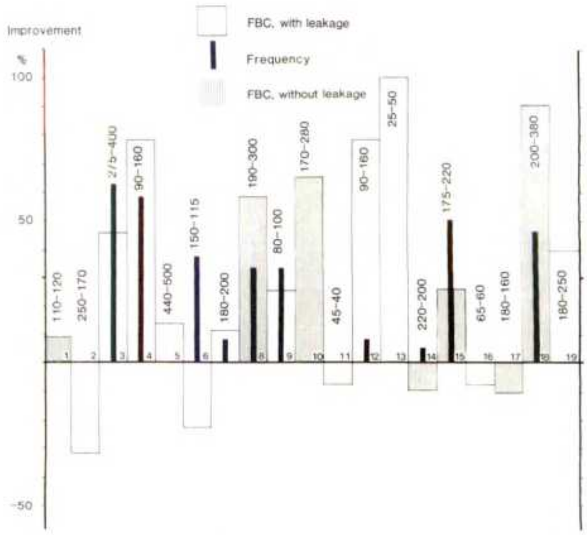

Fig. 2 Change in urodynamic parameters and micturition records obtained after external electrical stimulation in patients with UOB The bars reflect relative improvement; upward bars denote improvement and downward bars impairment. Hatched bars represent functional bladder capacity (FBC) of subjects able to inhibit micturition contractions; open bars represent those unable to do so. The FBC, as measured before and after treatment, is also indicated in terms of absolute volumes, represented by the figures about or within each bar. Solid bars represent the change in urinary frequency. Patient numbers are indicated at the base of each bar.

Five patients reported a poor response to stimulation with external electrodes. They and 3 others with early recurrence of symptoms (within 2 weeks) received further treatment in 4 sessions by direct pudendal nerve electrical stimulation: 5 reported a decrease in frequency and 4 showed an increase in bladder capacity. Two also had a negative Bors' test.

One male subject (11), who had had post-encephalitic bladder symptoms for 30 years, displayed a dramatic improvement with a 16-fold increase in bladder capacity; he regained the ability to inhibit micturition contractions and had a negative Bors' ice-water test. Frequency declined to less than one third and he was symptom-free 10 months after treatment.

In 4 patients there was no increase in bladder capacity but 1 (14) experienced relief of symptoms and a considerable decrease in frequency.

It should be noted that all 5 patients with a negative Bors' test following stimulation could inhibit bladder contractions; 4 of them also showed a reduction in frequency and an increase in bladder capacity.

The final result of external and supplementary needle stimulation was that 10 patients regained the ability to delay micturition following the sensation of urgency. The duration of this effect was variable, ranging from 2 days to 10 months (maximum follow-up). In most cases the duration was 3 to 6 weeks.

Since immediate bladder inhibition following the onset of electrical stimulation has been found to be more pronounced at high stimulation amplitudes, the duration of these effects was considered. The 6 female patients in the UOB group were included in efficiency vs. stimulation amplitude calculations, comparing the 2 sets of electrodes. The stimulation current amplitudes for vaginal and anal electrodes were averaged over the 4 sessions of stimulation for each subject. The percentage increase in bladder capacity and the percentage decrease in micturition frequency vs. current amplitude were plotted (Fig. 3). Linear regression of the plots was performed. The correlation coefficients for vaginal and anal stimulation versus functional bladder capacity were low (0.22 and 0.45 respectively), while the corresponding values for urinary frequency were higher (0.92 and 0.75 respectively). Thus the efficacy of stimulation appears more pronounced at high amplitudes.

Ten patients with idiopathic detrusor instability were stimulated by means of external electrode carriers only.

In most patients there was concomitant involuntary leakage at premature detrusor contractions. The bladder volume at desire to void was known as the functional bladder capacity. The Bors' ice-water test was negative in all subjects both before and after treatment.

As a result of MES, 7 of 10 patients developed an increase in bladder capacity and 6 had a decrease in micturition frequency. Four patients (21, 22, 25 and 28) regained voluntary inhibition of detrusor contractions after treatment and could also inhibit leakage. Three patients improved in all 3 parameters and a fourth regained the ability to inhibit detrusor contractions despite a decreased, although relatively large, bladder capacity. The improvement in bladder capacity, ranging from 150 to 600 ml before and from 150 to 550 ml after treatment, was 34% (average) with a standard deviation of 24%. Micturition frequency ranged from 6 to 22 times before and from 6 to 12 after stimulation. The improvement after treatment was 27% on average, with a standard deviation of 14% (Fig. 4).

No patient reported an increase in micturition frequency, *i.e.* stimulation did not increase bladder activity, although this has been reported by Janez *et al.* (1979). Patients who were able to control the micturition reflex before treatment retained this ability after treatment. No patient with a negative Bors' test developed a positive one. In addition, patients with uninhibited bladders and negative Bors' tests after stimulation displayed improvement in at least 2 of the other parameters.

There were no severe side effects. One female and 1 male patient reported increased bowel activity, probably the result of intra-anal stimula-

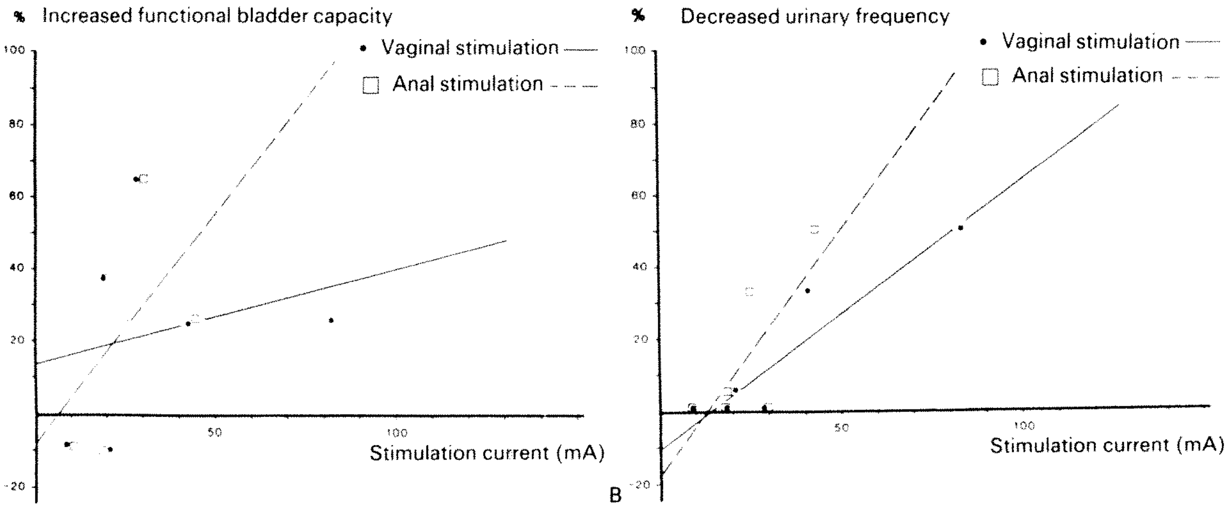

Fig. 3 Increased functional bladder capacity (A) and decreased micturition rate (B) versus stimulation current (mA) delivered by intravaginal and intra-anal electrodes in 6 female patients with UOB. The lines represent the linear regression of the samples.

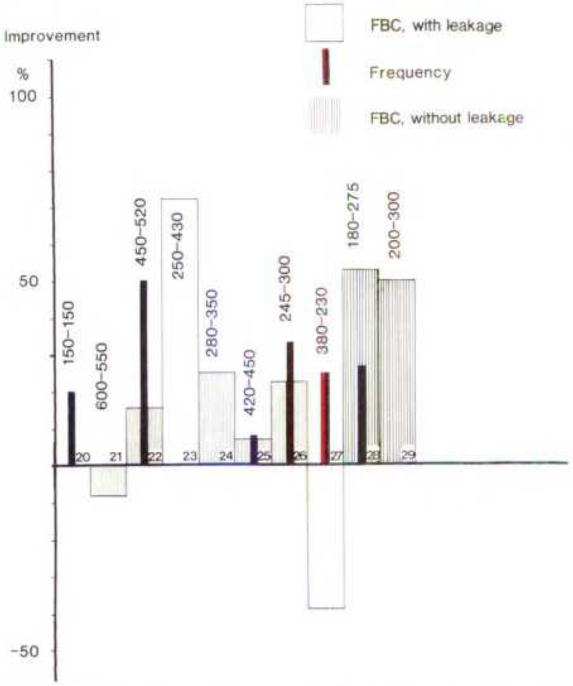

Fig. 4 Change in urodynamic parameters and micturition records measured before and after electrical stimulation with external electrodes in IDI. (Symbols as in Fig. 2.)

tion. One female patient developed a moderate paravaginal haematoma at the site of needle manipulations to reach the pudendal nerve. The haematoma resolved with no residual symptoms.

Using external electrodes, the changes in functional bladder capacity and micturition frequency were significant at the 95% level for the UOB group according to Students' *t* test. The IDI group displayed statistical significance at the 95% level for the change in micturition frequency only.

The non-parametric Wilcoxon signed rank test confirmed significance for the change in bladder capacity (95%) and micturition frequency (99%) for the UOB group. Again, only in IDI was micturition frequency altered at the 95% level.

Discussion

Experimental and clinical studies have shown that high stimulation amplitudes induce pronounced and lasting bladder inhibition. In the cat, inhibition lasts less than 1 h even when very high amplitudes—5 to 10 times the threshold voltage—are used (Lindström *et al.*, 1983, 1984; Ohlsson *et al.*, 1986). In the present study of patients with over-active bladders, long-lasting effects have been recorded, the duration of which increased progressively with the stimulation amplitude, an effect more strongly related to intra-anal than to intravaginal stimulation. An explanation can be found in the high sensibility of the anal region to stimulation (Ohlsson, 1987b). In the present study, however, intravaginal and intra-anal stimulation increased stepwise and in parallel. This implies that stimulation in the anus reached unpleasant levels more rapidly. At this point the upper limit for stimulation amplitude was defined, since the anal sensations were possibly used by the patients as an excuse to prevent any further increase in amplitude at either of the stimulation sites. In the further application of MES it is recommended that the stimulation amplitudes be increased in a parallel manner, enabling patients to perceive anal and vaginal stimulation equally during stepwise increases towards maximally tolerable amplitudes. Such a procedure is likely to improve the efficacy of the method. The scatter in tolerable stimulation amplitudes corresponds well with that found in a previous study of perception thresholds (Ohlsson, 1987b). MES also involves adaptation at the first perceived maximal tolerance level, which increases scattering. Since the stimulation amplitudes are limited by the patients' pain thresholds, optimal pulse parameters should be used to yield maximal inhibitory effects on the bladder. If sensibility is impaired, as in cases of spinal cord injury, effective stimulation can be obtained at supramaximal amplitudes despite suboptimal pulse parameters (Vereecken *et al.*, 1984).

MES produces relief of symptoms either immediately after treatment or up to a couple of days later. The effects lasted from 1 week to 10 months, as reported in other studies (Plevnik *et al.*, 1979; Janez *et al.*, 1982; Suhel *et al.*, 1982). Thus the response in humans differs from that obtained in animal experiments on artificially evoked overactivity. Compared with long-term treatment, there is a considerable discrepancy in the periods of treatment required to obtain a durable response (Fall, 1984). It has been suggested that the effect of stimulation is dependent on the degree of pelvic floor activation (Vereecken *et al.*, 1984). It should be noted that, in animal experiments, pudendal nerve stimulation does not alter the threshold for bladder inhibition (Lindström *et al.*, 1983). The degree of afferent pudendal nerve activation governs the bladder response and in sub-threshold, long-term stimulation, low intensity is compensated for by a longer stimulation time.

The pudendal nerve afferents are of major importance in bladder inhibition (Fall *et al.*, 1977a;

Lindström *et al.*, 1983, 1984). Stimulation very close to the pudendal nerve trunk should mediate impulses to the CNS more efficiently than stimulation using external electrodes. This was confirmed in some patients for whom stimulation with external electrode carriers induced no bladder inhibition, while with direct stimulation of afferent pudendal nerves the sensation of stimulation was no longer a guide to indicate adequate stimulation. The first sensation of direct pudendal nerve stimulation coincided well with the onset of pulsating motions of the needle electrode owing to unilateral pelvic floor contraction.

The patients presenting inconsistent data concerning frequency of micturition and bladder capacity may cause confusion. The UOB group is a difficult one to study since age and memory defects can impair patients' adherence to the protocol. However, this syndrome is frequent, very troublesome to the patient and expensive for society. Trials have to be made and some imperfections must be accepted. However, there are comments which should be made on the design of the study. There is a rational explanation for the finding that some patients showed no rise in bladder capacity but recorded a decrease in micturition frequency. Cystometry was performed 1 month after treatment but the frequency of micturition was recorded within 1 week of stimulation. This implies that improvement could have genuinely occurred but declined again by the time of cystometry. Such short durations have also been recorded by Suhel *et al.* (1982). Furthermore, cystometry seems to be a blunt instrument to record therapeutic effects on the overactive bladder, while micturition charts give more reliable information (Tapp *et al.*, 1987). The patients with improved bladder capacity after treatment according to cystometry, but with no improvement according to their micturition charts, are probably further examples of this theory. An increased bladder capacity, as measured by cystometry, may not always imply that the patient has recovered in every-day life. On the contrary, in previous trials, normalisation of urodynamic parameters correlated with symptomatic improvement but was no absolute prerequisite for clinical recovery (Fall, 1984; Fall *et al.*, 1986; Eriksen *et al.*, 1987).

In the treatment of IDI, maximal electrical stimulation should be considered as an alternative to long-term electrical stimulation. Empirically, the UOB is incurable and seldom adequately controlled. Despite the difficulties in assessing the objective or semi-objective parameters in this population, the results in this pilot study are sufficiently encouraging to warrant further studies, since MES is one of the few options available. For some patients it is more convenient to undergo treatment over a limited period of time. A major drawback of maximal electrical stimulation is the high consumption of clinical and technical resources. The patient must be attended by a specialised team in a room that might be used for other clinical procedures. Home treatment with maximal electrical stimulation has been suggested and good results have been reported (Plevnik *et al.*, 1986). Further technical developments are expected, with the aim of finding the best way of stimulating the appropriate nerves for the desired effect (Fall, 1985).

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Urinary Bladder Cortical Evoked Potentials in Man: Suitable Stimulation Techniques

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Summary—A practical and easily applicable method of recording cortical potentials evoked by bipolar electrical stimulation of the bladder wall is described. This constitutes an objective electrophysiological test of afferent bladder central projections.

Comparison of bipolar and monopolar methods of intravesical stimulation led to the conclusion that the simpler monopolar intravesical electrode technique is unsuitable because it yields potentials contaminated by extravesical components.

Among the various electrophysiological methods that have been investigated in order to evaluate the sensory afferents of the lower urinary tract are cortical potentials evoked by electrical stimulation of various peripheral urinary structures (Gerstenberg *et al.*, 1981; Kaplan, 1981; Haldeman *et al.*, 1982; Opsomer *et al.*, 1986; Sarica and Karacan, 1988).

In 1982, Badr *et al.* demonstrated the existence of well defined cortical potentials evoked by electrical monopolar stimulation of the bladder wall. This was a promising step towards developing a neurophysiological test of the peripheral and central pathways responsible for sensations of bladder distension. Nevertheless, Badr *et al.* remained cautious about the exact origin and nature of the evoked responses.

The present study has addressed this unresolved issue and extended the observations of Badr *et al.* (1982). In order to devise a method that was simple and capable of being applied routinely, it was important to confirm the validity of the monopolar stimulation technique.

Patients and Methods

Twenty-five patients (22 women and 3 men) with either genuine stress incontinence and normal cystometry or urge incontinence with uninhibited bladders gave consent for recording bladder evoked potentials during cystoscopic examination. Their ages ranged from 22 to 86 years; 23 had a well defined stable lateralised ischaemic hemispheric cerebral infarct documented by CT scan; the other 2 were neurologically normal.

The patients were placed in the gynaecological position and made as comfortable as possible in order to induce relaxation. Stimulation electrodes (length 1 m) were constructed from 0.75 mm insulated steel wire with sharpened tips. These were implanted behind the trigone to a depth of 0.3 cm and 1 to 2 cm apart; the procedure was done under visual control via a rigid cystoscope equipped with an Albaran's lever. The endoscope was then removed and the electrodes left in place for bladder stimulation. Inter-electrode impedance measurement checked correct implantation and absence of short circuit.

For monopolar bladder stimulation, a conventional surface stimulation electrode was placed on the anterior thigh. This acted as the anode and one of the implanted needles served as the stimulating cathode. Care was taken to maintain the stimulus intensity below any detectable muscle thigh twitch threshold.

Potentials evoked by bipolar and monopolar stimulation according to Badr *et al.* (1982) were systematically compared. Electrical rectangular

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stimulation pulses of 200 ms duration and 10 to 20 mA intensity were delivered at a regular rate between 1 and 2 Hz until the averaging process had sufficiently enhanced the signal to noise ratio.

A commercial signal averager equipped with an artefact rejection system (Nicolet Pathfinder II) was used. The amplified scalp signal recorded from the vertex with a frontal midline (Fpz) reference was filtered with a bandpass of 5 to 250 Hz (attenuation slope beyond the cut-off frequencies: 12 dB/octave).

Results

Systematic differences between the waveforms evoked by bipolar and monopolar stimulation were noted: potentials evoked by monopolar stimulation were better defined, contained more deflections at shorter latencies and in 82% of patients the amplitudes were greater than those evoked by bipolar stimulation.

Figures 1 and 2 show the differences between evoked potentials following bipolar and monopolar stimulation.

Figure 1 shows 5 consecutive tracings in a neurologically normal 48-year-old woman who was eventually diagnosed as having genuine stress incontinence. A1 and A2 superimposed waveforms are separate averages of 400 sweeps each, obtained after bipolar intravesical stimulation. They are limited to a slow negative wave peaking at 108.4 ms. The A3 waveform is the grand average of the two lower traces. The A4 trace shows the morphology of cortical activity recorded (200 sweeps) after conventional bipolar electrical stimulation of the right lateral popliteal nerve at the head of the fibula, with the same recording parameters as for the previous traces. The P40 component peaks at 34 ms, well within the 2.5 SD confidence interval for the subject's height (156 cm). The A5 waveform was obtained after monopolar intravesical stimulation (200 sweeps) with the anode in the centre of the anterior aspect of the thigh and contains definite earlier components (occurring between 20 and 60 ms). The more prominent late negative wave has a shorter (N83.6) peak latency than its bipolar counterpart (N108.4).

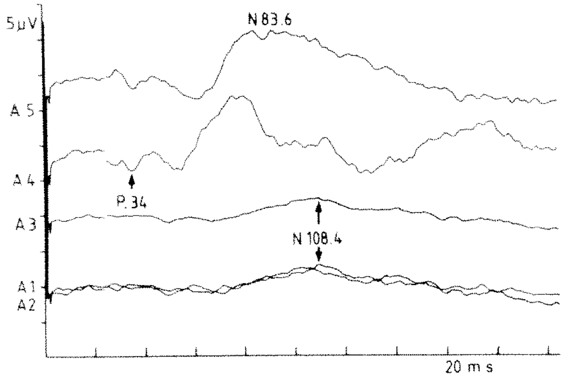

Fig. 1 Bladder evoked potentials obtained from a neurologically normal 48-year-old woman. A1/A2: superimposed separate successive evoked waveforms obtained after bipolar intravesical stimulation. A3: grand average obtained by adding up and scaling A1 and A2 waveforms. A4: waveform evoked after stimulation of right lateral popliteal nerve at the head of the fibula. A5 waveform evoked after monopolar intravesical stimulation; stimulating anode on thigh. Horizontal calibration 20 ms. Vertical calibration 5 µV.

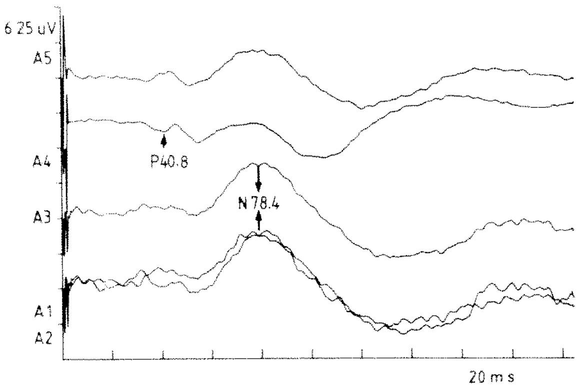

Fig. 2 Bladder evoked potentials obtained from a 66-year-old woman with a right-sided ischaemic infarct in the sylvian artery territory. A1/A2: superimposed separate successive evoked waveforms obtained after bipolar intravesical stimulation. A3: grand average obtained by adding up and scaling A1 and A2 waveforms. A4: waveform evoked after stimulation of right lateral popliteal nerve at the head of the fibula. A5: waveform evoked after monopolar intravesical stimulation; stimulating anode on thigh. Horizontal calibration 20 ms. Vertical calibration 6.25 µV.

Figure 2 shows the results of the same procedure in a 66-year-old woman with a left hemiparesis due to a cerebral infarct in the vascular territory of the right sylvian artery. The superimposed A1 and A2 waveforms were evoked by 2 successive runs (100 sweeps each) of bipolar bladder wall stimuli. They are made of a single negative peak with a latency of 78.4 ms. In A4, the P40 component (obtained after conventional right popliteal nerve stimulation; 400 sweeps) is in the normal range for the patient's height (40.8 ms; 164 cm). The A5 waveform (monopolar bladder wall stimulation; 300 sweeps) shows the occurrence of an early component (P34–N43.2 ms) that is clearly associated with the waveform evoked by popliteal nerve stimulation but not with the one evoked by bipolar bladder wall stimulation.

To assess this suspected contamination of the monopolar bladder evoked potential by early components originating in extravesical structures, the waveforms obtained in 4 patients with 3 different anode locations were compared.

Figure 3 illustrates this comparison for 1 patient. All 3 traces are the average of 400 sweeps; the A1 trace is the bipolar evoked potential, made of a slow negativity on which 3 negative peaks (N90, N116, N146) are superimposed. The A2 monopolar trace was evoked with the anode on the right ankle. The effects of monopolar intravesical stimulation, *i.e.* the appearance of short latency positive peaks and the shortening of the main negative component latency, were readily obtained. The A3 tracing was obtained by placing the anode more proximally on the knee, leading to a clear-cut shift of all evoked components towards shorter latencies. This effect would be unexpected if the putative bladder evoked potential were caused exclusively by stimulation of bladder wall structures in the vicinity of the implanted cathode.

Reproducible waveforms were evoked by bipolar intravesical stimulation in 23 of 25 patients. Their sole reliably identifiable component took the form (Figs 1 and 2, tracings A3) of a vertex negative wave with a mean peak latency of 96.3 ms, a standard deviation of 9.88 ms, a range of 70 to 110 ms and a mode of 100 ms. This component has therefore been labelled N100 (Donchin, 1977).

Discussion

The development of stimulation electrodes that allow easy positioning under visual control and the subsequent removal of the cystoscope provides a simple and comfortable technique. The stimulating electrodes have sufficient rigidity to allow precise guiding out of the cystoscope, but are not so inflexible as to oppose the gentle movement required to remove the endoscope, leaving them in place. The sharpened tips, stripped of the polyvinylchloride insulation, are gently pushed through the inner wall of the bladder until slight resistance is felt. This indicates that the larger diameter of the insulating material is impinging on the mucosa and that the bare tip has penetrated the bladder wall to a depth of 0.3 cm. This allows good anchorage without the risk of puncturing the full thickness of the bladder wall.

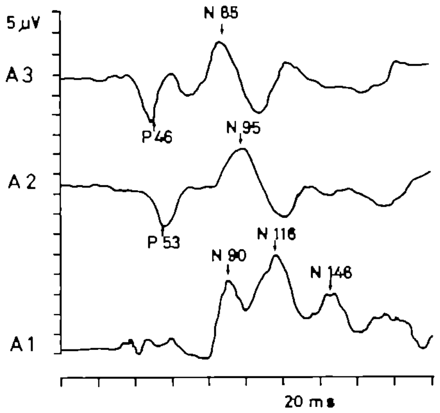

Fig. 3 Contamination effect of monopolar technique revealed by moving the anode A1 waveform evoked after bipolar stimulation A2. waveform evoked after monopolar stimulation: anode at the ankle. Note the appearance of a P53 component as well as the latency decrease of the main negative wave from N116 to N95 A3 waveform evoked after monopolar stimulation; anode at the knee This more proximal location of the anode produced the same general waveform as A2 but with a shift towards shorter latencies: from N90 to N85 and from P53 to P46 Horizontal calibration 20 ms. Vertical calibration 5 µV

Apart from the usual differences in handling the cystoscope, electrode placement proved as easy in men as in women.

Provision for removal of the cystoscope during the procedure makes the recording more comfortable for the patient and reduces major artefact sources, *i.e.* muscular activity resulting from the patient's discomfort and electromagnetic interference from endoscopic light sources.

The finding that the monopolar method of bladder stimulation yields shorter latency cortical potentials than those evoked by the bipolar technique is not surprising. In the monopolar condition, the stimulating current flow between cathode and anode is likely to impinge on several electrically excitable structures. Sarica and Karacan (1988) showed that the proximal and distal urethra are innervated by different peripheral afferents, selective stimulation of which yields cortical evoked potentials of different latency and morphology. These differences are similar (Fig. 1) to those presently observed between the results of mono- and bi-polar bladder wall stimulation. The waveforms obtained by stimulation of the vesicourethral junction and the prostatic urethra are made of a prominent negativity with peak latencies ranging respectively between 84 and 104 ms (mean 94.9 ± 6.5) and between 75 and 115 ms (mean 96.5 ± 10.9).

The latter latencies are similar to those of the N100 peak obtained after bipolar bladder wall stimulation.

Although it is difficult to assess how the N100 latencies obtained in the present study were influenced by the cerebral lesions that were present in all but 2 patients, the similarity between the latency distributions of the bladder N100 and of the first negative peak obtained by Sarica and Karacan (1988) after stimulation of the prostatic urethra in normal subjects suggests that such an interference must have been minor. If the cerebral lesion had an effect on N100 latency in a certain proportion of patients, an extension of the latency range towards higher values would be expected. This does not seem to have been the case, since Sarica and Karacan's data indicate that the inter-individual variability of somatosensory evoked potentials mediated by pelvic afferents is already high in normal subjects, and of a range and magnitude similar to that of the bladder N100 which is presumably mediated by pelvic and hypogastric afferents (Badr *et al.*, 1982).

It was concluded that the monopolar intravesical stimulation method is unsuitable for investigation of the urinary bladder sensory cortical projections. If the bipolar stimulation technique appears more suitable, the question of which sensory structures are involved in the responses remains unanswered.

Now that a relatively easy method of electrical bladder stimulation has been established, its value in the assessment of neuro-urological patients will have to be determined.

Although convenient to use, electrical stimulation of the bladder wall excites several (extero- and proprio-ceptive) types of sensory receptors or fibres (Bradley and Sundin, 1982) which project centrally via both dorsal columns and spinothalamic tracts. It would be interesting to study the various sensory modalities separately, in order to define their roles in the mechanism of continence. A further step would be to obtain cortical potentials evoked in response to mechanical bladder distension, a much more physiological way of probing the afferent vesical pathways.

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Sequential Morphological Changes in the Pig Detrusor in Response to Chronic Partial Urethral Obstruction

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Summary—The sequential morphological changes which occur in the wall of the porcine urinary bladder in response to experimentally induced partial outflow obstruction have been determined using morphometric light and electron microscope techniques. The initial morphological response to urethral obstruction was a reduction of approximately 50% in the density of autonomic nerves in the bladder wall which occurred within the first 3 months. During this period the morphology of smooth muscle cells and the distribution of connective tissue were unaltered. Longer periods of obstruction produced a gradual further reduction in the density of innervation. However, from 3 months onwards the detrusor muscle bundles became infiltrated by connective tissue, although significant change in muscle cell size was not detected after obstruction for 12 months. Using electron microscopy, smooth muscle cells were observed to possess extensive amounts of perinuclear granular reticulum, this feature being particularly marked in bladders subjected to longer periods of obstruction. The underlying mechanisms responsible for these structural changes remain to be determined.

Previous studies of the human urinary bladder have demonstrated that marked histological changes occur in response to outflow obstruction. These changes include smooth muscle cell hypertrophy (Gilpin *et al.*, 1985), infiltration of muscle bundles by connective tissue (Gosling and Dixon, 1980) and a decrease in the density of nerves associated with the detrusor muscle (Gosling *et al.*, 1986). However, the chronological sequence in which these structural alterations occur is difficult to determine using human material since bladder biopsies are obtained from different patients in whom the time interval during which obstruction has been present is unknown. Consequently an animal model has been developed using the experimentally obstructed urinary bladder of the pig. The sequence of morphological changes occurring in the bladder wall of individual animals as a result of partial urethral occlusion has then been studied using light and electron microscopy.

The results of concurrent pharmacological studies on samples of detrusor muscle from this group of animals have been reported elsewhere (Speakman *et al.*, 1987).

Materials and Methods

The detailed surgical procedure for inducing partial bladder outflow obstruction in Landrace pigs has been previously described (Speakman *et al.*, 1987). The method involved the insertion of a silver ring around the proximal urethra in a group of recently weaned Landrace pigs, each weighing 10 to 15 kg. The rings were horseshoe-shaped with a loop at each end, allowing the ends to be approximated using a silk ligature after placement around the urethra under general anaesthesia. With subsequent normal growth of the pig a progressive obstruction was produced. Following this procedure 2 animals developed chronic retention, whereupon their silver rings were removed. Full thickness bladder biopsies were obtained from the anterior wall of the bladder

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at the time of the initial operation (in 5 pigs) and at various times thereafter. When subsequent biopsies were obtained, care was taken to avoid scar tissue which had formed around the site of the previous biopsy. Thus each of the 7 experimental animals included in this study provided at least 2 sequential biopsies (Table 1), while 4 animals had sham operations and served as controls. Each biopsy was divided into 2, 1 piece being processed for light microscopy and 1 for electron microscopy.

Tissue preparation for light microscopy

Each tissue sample was rapidly frozen in 2-methylbutane cooled in liquid nitrogen, transferred to a cryostat and serially sectioned at 10 μm. Alternate sections were stained either for routine histology using Masson's trichrome stain or processed to demonstrate acetylcholinesterase (AChE)-containing nerves using a modified Gomori method (Gomori, 1952).

Tissue preparation for electron microscopy

Each tissue sample was further subdivided into 1 mm^3 pieces and fixed in 2.5% glutaraldehyde in sodium cacodylate buffer at 4°C for 2 to 10 h. After washing in cacodylate buffer alone the tissue pieces were post-fixed in buffered osmium tetroxide. Following a further wash in buffer alone the tissue samples were stained *en bloc* with 2% aqueous uranyl acetate before dehydration in ascending concentrations of acetone and embedding in epoxy resin. Thin sections were double stained with alcoholic uranyl acetate and lead citrate prior to examination in a Philips EM300 electron microscope.

Table 1 Obstructed Animals

Pig	*Duration of obstruction*	*% muscle (±SE)*	*MPA (±SE) (μm^2)*	*Amount of AChE positive nerve/mm^2 (±SE) (corrected)*
A	3 months	75 (±1)	75 (±5)	23 (±2)
	6 months	68 (±1)	55 (±3)	9 (±2)
B	0	70 (±1)	42 (±4)	108 (±5)
	6 weeks	71 (±1)	44 (±2)	77 (±4)
	7 months	66 (±1)	35 (±2)	24 (±2)
C	0	71 (±2)	42 (±2)	188 (±9)
	2 months	72 (±1)	68 (±3)	96 (±9)
D	0	72 (±2)	42 (±2)	117 (±8)
	3 months	71 (±2)	59 (±2)	76 (±5)
E	0	69 (±2)	45 (±6)	170 (±6)
	2 months	73 (±1)	58 (±3)	87 (±5)
	14 months	58 (±1)	51 (±8)	39 (±4)
F	0	71 (±2)	49 (±4)	97 (±4)
	2 months	73 (±1)	50 (±3)	62 (±4)
	9 months	65 (±2)	51 (±2)	40 (±3)
G	2 weeks	74 (±1)	46 (±4)	75 (±4)
	6 weeks	72 (±2)	42 (±2)	8 (±1)

Quantitative methods for light microscopy

(a) Amount of muscle/mm^2 of tissue. The amount of muscle within a given area of each sample was determined using a point counting technique (Williams, 1977). Using a ×40 objective, multiple non-overlapping fields were assessed with an eye piece graticule consisting of a lattice of 100 squares, giving 121 points where lines intersected. The number of fields counted depended on the size of the biopsy section and was always more than 5 (*i.e.* over 600 points) and more often 10 (*i.e.* 1200 points). The mean value of muscle per unit area was expressed as a percentage for each biopsy (Tables 1 and 2).

Table 2 Control Animals

Pig	*Age*	*% muscle (±SE)*	*MPA (±SE) (μm^2)*	*Amount of AChE positive nerve/mm^2 (±SE) (corrected)*
H	6 weeks	73 (±2)	53 (±2)	100 (±3)
	12 months	70 (±3)	48 (±3)	95 (±8)
I	2 months	69 (±2)	51 (±2)	96 (±7)
	12 months	70 (±3)	46 (±3)	84 (±3)
J	6 weeks	77 (±2)	52 (±3)	132 (±7)
	9 months	74 (±1)	50 (±2)	120 (±6)
K	6 weeks	73 (±2)	49 (±3)	92 (±5)
	3 months	69 (±1)	42 (±4)	91 (±9)
	7 months	75 (±1)	35 (±2)	85 (±5)

(b) Amount of nerve/mm^2 of tissue. Sections stained to demonstrate acetylcholinesterase-containing nerves were examined using the same magnification and the same eyepiece graticule as above. Counts were made of the number of grid intersections which overlay enzyme-positive nerve fibres. Multiple non-overlapping fields were selected so as to include the entire area of smooth muscle in one section from each biopsy. The amount of nerve/mm^2 of tissue was then converted into the amount of nerve/mm^2 of muscle for each biopsy examined (Tables 1 and 2).

(c) Mean profile area (MPA). Photomicrographs of transversely sectioned smooth muscle cells were prepared and the total area of smooth muscle determined using a point scoring technique. This area was then divided by the actual number of cells

present to determine the mean muscle cell profile area (MPA) for each sample.

Results

Each experimental animal provided at least 2 bladder samples removed at different times after urethral surgery (Table 1). Quantitative values for the amount of AChE-positive nerve/mm^2 of detrusor muscle in each biopsy are shown in Figure 1. In each case the actual value for the amount of AChE-positive nerve/mm^2 of detrusor muscle obtained by point-counting was corrected for possible change in muscle cell size by multiplying it by the ratio of the MPA for that animal to the MPA of the control animals, which was $46 \pm 3\ \mu m^2$ (mean ± SEM). Values for the 4 sham operated control animals are shown in Figure 2.

From Figure 1 it may be seen that a marked reduction in nerve density within the detrusor muscle occurred during the first 3 months after urethral obstruction. The mean value for the amount of AChE-positive nerve/mm^2 of detrusor muscle for control animals was 119 ± 9 (SEM), whereas 3 months after placement of the silver rings this value had reduced to 63 ± 4. With longer periods of partial urethral occlusion the density of innervation was further reduced to a value of 28 ± 7 at 12 months after the initial operation. The quantitative value for the amount of nerve/mm^2 of detrusor muscle obtained for each biopsy is the average value obtained from examining a large number of muscle bundles. However, in most of the biopsies examined, variation in the density of innervation was observed between one muscle bundle and another. During the initial 3-month period, axons with fine structural features characteristic of degeneration were observed in some biopsies using electron microscopy (Fig. 3). However, the smooth muscle cells of these biopsies retained normal fine structural features and the amount of intercellular connective tissue was similar to that of control samples. Bladder biopsies removed between 3 and 14 months after obstruction

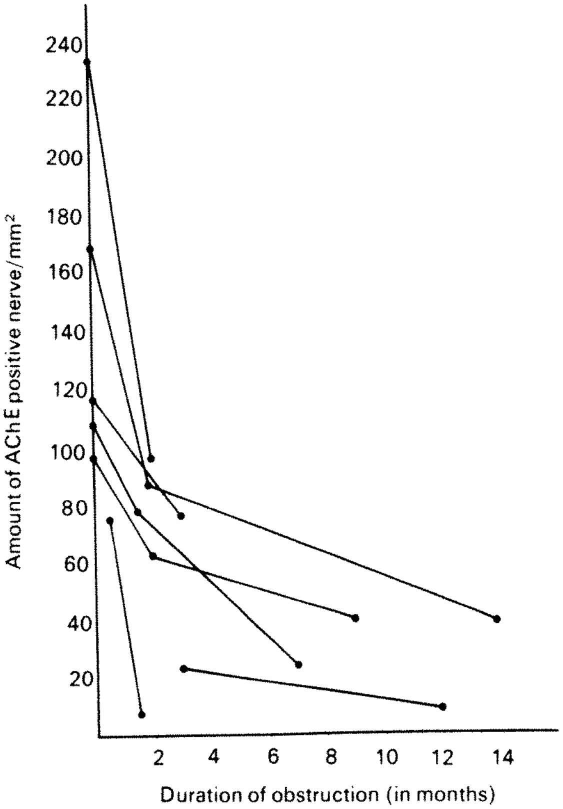

Fig. 1 Data from obstructed animals showing the amount of AChE-positive nerve/mm^2 of detrusor muscle obtained for each biopsy. Values obtained for successive biopsies from the same animal are joined by a straight line.

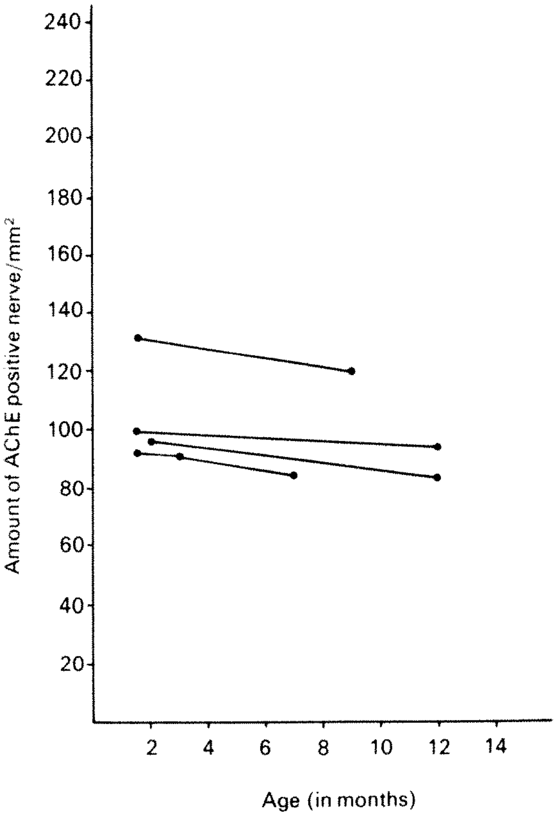

Fig. 2 Data from control animals showing the amount of AChE-positive nerve/mm^2 of detrusor muscle at different ages.

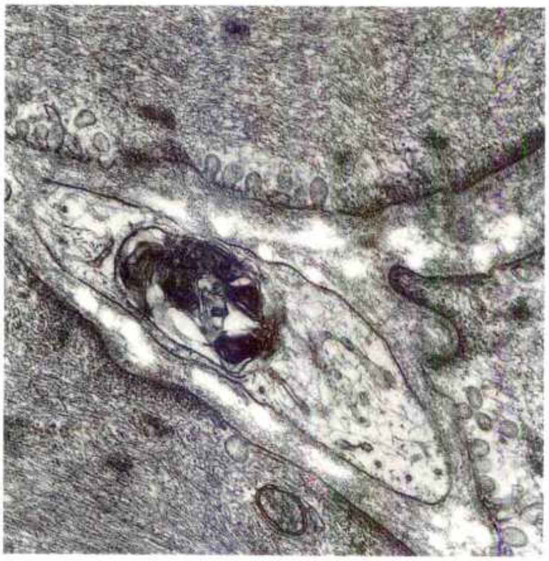

Fig. 3 Electron micrograph of a degenerating nerve terminal observed in a biopsy obtained 6 weeks after urethral obstruction. (×45,000).

contained increased quantities of interfascicular and intrafascicular connective tissue compared with control biopsies. Connective tissue infiltration was more marked in bladder samples removed at longer times after urethral obstruction (Fig. 4). In the electron microscope these connective tissue elements consisted of small clusters of collagen fibrils together with randomly scattered amorphous elastic fibres. Furthermore, smooth muscle cells in some samples obtained 3 to 14 months after partial obstruction displayed alterations in their staining characteristics and in their fine structure. In the light microscope many smooth muscle cells displayed a pale-staining perinuclear region surrounded by darker staining cytoplasm. In the electron microscope, smooth muscle cells were observed with increased amounts of perinuclear rough endoplasmic reticulum while the myofilaments and dense bodies of such cells were confined to the periphery (Fig. 5). In many instances the myofilaments appeared condensed into a ring or halo which surrounded the perinuclear granular cisternae and mitochondria (Figs 4 and 5). Cells of this type presumably correspond to those with a pale-staining central region and a dark-staining periphery observed in the light microscope. In samples obtained 12 and 14 months after urethral obstruction, some detrusor smooth muscle cells possessed an extensive granular reticulum with dilated cisternae while occasional bundles of fine filaments were discernible towards the cells' periphery (Fig. 6). While such cells resembled fibroblasts in their content of granular reticulum, each retained a complete investment of basal lamina material

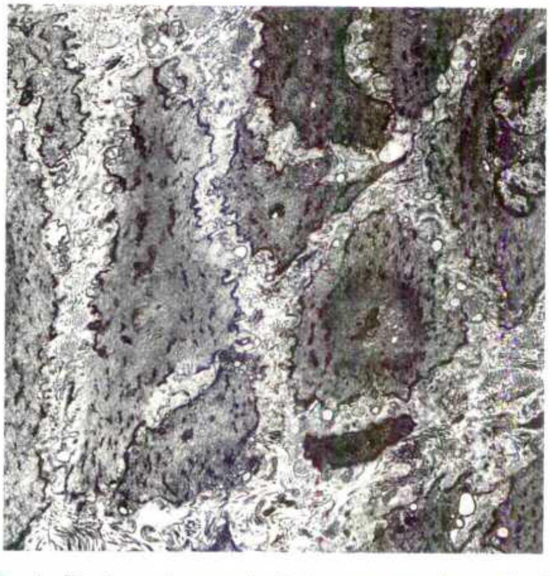

Fig. 4 Electron micrograph of detrusor smooth muscle 12 months after urethral obstruction. Individual cells are separated from their neighbours by collagen and elastic fibres. Note the perinuclear halo of condensed myofilaments in two of the smooth muscle cells. (×4,500).

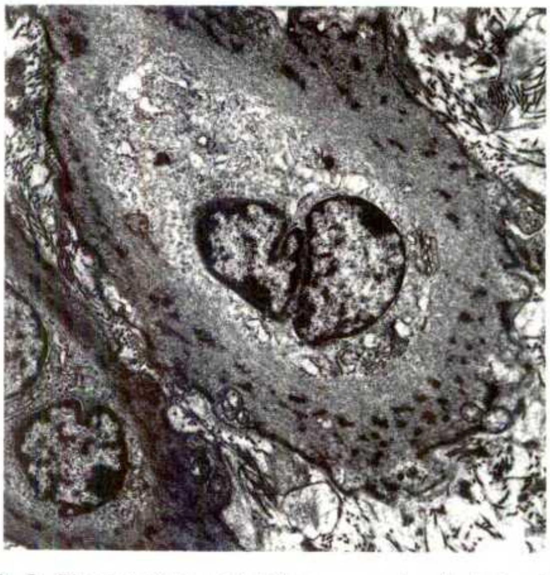

Fig. 5 Electron micrograph of detrusor muscle cells obtained 4 months after urethral obstruction. Rough endoplasmic reticulum occupies the perinuclear sarcoplasm while myofilaments and dense bodies are confined to the cells' periphery. (×11,300).

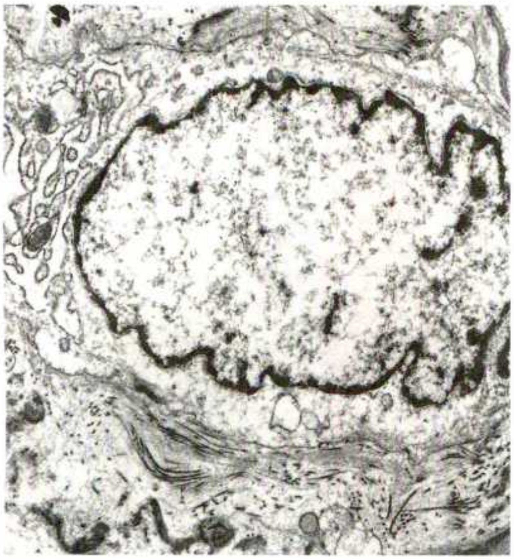

Fig. 6 This much altered detrusor smooth muscle cell observed 12 months after urethral obstruction has a well developed granular reticulum and thus resembles a fibroblast. However, the investing basal lamina is still evident while bundles of myofilaments may be seen in some regions of the cell. (× 8,800).

and was thus identified as a muscle cell, albeit with a much altered fine structure.

Discussion

Smooth muscle hypertrophy, infiltration of the detrusor muscle by connective tissue and a reduction in the density of autonomic innervation have all been reported to occur in the human bladder wall in cases of bladder outflow obstruction (Gosling and Dixon, 1980; Gilpin *et al.*, 1985; Gosling *et al.*, 1986). These morphological changes have been reported in bladder biopsies removed at the time of prostatic resection. However, in such patients the length of time during which the obstruction was present prior to the operation was unknown and thus the precise sequence of morphological change in the bladder wall in response to obstruction cannot be deduced from such studies. By using an animal model in which the onset of urethral obstruction can be more accurately determined it was hoped to gain insight into the chronological sequence in which structural changes occur in the bladder wall.

The results of the present study have shown that the initial response to acute bladder outflow obstruction in the pig is a rapid reduction in the density of autonomic nerves associated with the detrusor muscle. Confirmation of axonal degeneration was obtained by electron microscopy in several of the biopsies removed from 6 weeks to 3 months after the production of partial urethral obstruction. Although there was considerable variation in the density of innervation from animal to animal, the reduction in the amount of nerve 3 months after obstruction was approximately 50% in each case. This innervation density was reduced by a further 50% after 12 months' obstruction. It is generally accepted that normal detrusor muscle is richly innervated, the ratio of nerve axons to smooth muscle cells being of the order of 1:1 for both the pig (unpublished observation) and the human bladder (Daniel *et al.*, 1983). Although a 75% reduction in nerve is considerable in numerical terms, the chronically obstructed bladder retains a substantial degree of innervation and this residual innervation is presumably sufficient to initiate muscular contraction during micturition.

The method employed to quantify the innervation density gives an average value for those muscle bundles included in the selected fields of view and so it is desirable to count as many fields as the size of the tissue section will allow in order to obtain as accurate an estimate as possible. However, it must be emphasised that the reduction in innervation was not uniform throughout the detrusor, but varied from muscle bundle to muscle bundle. Thus some detrusor muscle bundles were relatively poorly innervated by AChE-positive nerves after 3 months of partial urethral obstruction, but other bundles still retained considerable numbers of nerve fibres. This observation may be significant in explaining the aetiology of detrusor muscle denervation, possibly being related to differing degrees of tissue hypoxia or to differences in wall tension that may occur between one muscle bundle and another.

During the first 3 months following the onset of obstruction the morphology of smooth muscle and connective tissue appeared unchanged, but from 3 months onwards there was a gradual infiltration of detrusor muscle bundles by connective tissue. In addition, many of the smooth muscle cells displayed alterations in their fine structure, the perinuclear region becoming occupied by an extensive granular reticulum often surrounded by a ring of tightly packed myofilaments. These alterations in smooth muscle cell morphology, together with increased amounts of intercellular connective tissue, were more marked in biopsies obtained after longer periods of outflow obstruction, being most pronounced at 12 and 14 months in the present work.

By this time some detrusor muscle cells adopted a "fibroblast-like" appearance with regard to their content of granular reticulum, although they still retained their investing basal lamina and were thus identified as smooth muscle cells. The additional connective tissue elements in the form of collagen and elastic fibres were laid down both around and within the detrusor muscle bundles, so that in some bundles every smooth muscle cell was separated from its neighbours by connective tissue. In view of this and the clear evidence of increased amounts of protein synthesising apparatus within the detrusor muscle cells, it seems likely that smooth muscle cells are responsible for the manufacture of the connective tissue elements which gradually infiltrate the bladder wall in response to longer periods of outflow obstruction. In this context the synthesis and secretion of connective tissue proteins by smooth muscle cells has been previously described in other organs (Ross and Klebanoff, 1971).

It is of note that no significant hypertrophy of detrusor smooth muscle cells was detected after 12 months' obstruction, although muscle cell hypertrophy has been reported in the obstructed human bladder (Gosling *et al.*, 1986). The reason for this difference may relate to the relatively short period during which partial urethral occlusion was established in the present series of experimental animals or may be due to the particular animal model employed. It has to be acknowledged that a young animal "growing into the obstruction" may not truly represent the situation of an older male whose growth phase is past and whose response to outflow tract obstruction may be rather different. Concerning the possibility of smooth muscle cell hyperplasia, mitotic figures were not observed in any of the specimens examined, thus failing to confirm that detrusor smooth muscle cells increase in number in response to urethral occlusion.

Finally, it must be emphasised that the degree of obstruction produced by the method employed in the present study is difficult to determine for individual animals. However, it is possible that those animals subjected to relatively severe urethral obstruction were those showing the most marked changes in the bladder wall with regard to reduced numbers of autonomic nerves and infiltration by connective tissue. Having determined the progression of morphological change in response to outflow obstruction, studies are now in progress to determine whether such alterations are reversed by removal of the urethral obstruction.

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Bladder Irrigation or Irritation?

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Summary—Exfoliation rates of urothelial cells following bladder irrigation were studied in patients with long-term indwelling catheters and chronic urinary tract infections (UTI). The irrigations were associated with an increased shedding of urothelial cells. Ultrastructural studies of these cells demonstrated increased disruption when compared with those obtained from normal subjects without catheters or chronic infection. The findings suggest that bladder irrigation further damages the already disrupted urothelium, which may in turn increase the predisposition of the bladder to the recurrent infections, commonly associated with patients who have indwelling urinary catheters. Bladder irrigation methods and the indications for their use require reassessment.

The importance of catheter-associated urinary tract infections as a cause of morbidity and mortality has been well documented (Feingold, 1970; Macfarlane, 1985). Clinicians and microbiologists have tried to overcome this problem by improving the prevention, control and treatment of these infections. Such approaches have included the avoidance of unnecessary catheterisation, the use of closed sterile drainage and the observance of aseptic techniques in catheter handling. These measures have reduced the incidence or delayed the onset of catheter associated infections but have failed to eradicate the problem completely. Another common but more controversial method used in the prevention and treatment of catheter-associated infections is bladder irrigation. In some reports bladder irrigation has been shown to be effective (Merimsky *et al.*, 1981; Davies *et al.*, 1987), whereas in others they were of questionable value (George and Healing, 1977; Elliott *et al.*, 1985). Other studies have demonstrated that urinary catheterisation with chronic urinary tract infections, a common indication for bladder irrigation, results in disruption of the urothelium (Ekelund and Johansson, 1979) with increased shedding of urothelial cells into the urine (Elliott *et al.*, 1985, 1986a). The mucosa is an important host defence against the development of infection and should the urothelium be damaged during long-term catheterisation and chronic UTI, it is possible that bladder irrigation may further disrupt the mucosa and so predispose these patients to repeated microbial invasion. In preliminary studies we have shown that urothelial damage occurs after bladder washouts (Elliott *et al.*, 1986b, 1987). We now report the results of 2 investigations on the effect of bladder washouts on the urothelium.

Patients and Methods

Controls

In order to ascertain normal urothelial exfoliation rates, mid-stream specimens of urine from 30 normal adult males (average age 24 years) were examined. A further control group included 20 female patients (average age 75 years) who had long-term (>6 months) indwelling catheters with associated UTI and who had not received any bladder irrigation. Five fresh catheter specimens of urine collected from these patients on consecutive days at mid-morning were examined.

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Prospective study

Five female patients (average age 72 years) with long-term indwelling urinary catheters (average duration 9 months) were randomly selected. Freshly passed catheter urine samples were collected aseptically for up to 18 consecutive days from all patients. During this period, as part of their management, 2 patients underwent chlorhexidine and 3 underwent noxythiolin intermittent bladder irrigations. These were performed by slowly instilling approximately 30 to 60 ml chlorhexidine (0.02%) or noxythiolin (2.5%). The irrigant fluid was left in the bladder for up to 30 min and then allowed to drain out. All patients received 4 or 5 washouts during the study. Following washout, urine samples were obtained after residual irrigation fluid had been passed.

Cross-over study

The effect of bladder irrigation on urothelial exfoliation was also studied in a further 9 patients (4 female, 5 male, average age 76 years), all of whom had long-term indwelling urinary catheters. All underwent irrigation with 2.5% noxythiolin, and 7 with physiological saline. The solutions used for the washouts were selected randomly and 7 patients received both types of irrigation, with an interval of 2 to 6 weeks between each procedure. The washouts were carried out in a similar manner to those of the prospective study. Urine samples were obtained from each patient before and immediately after the washout. The first urine samples after the washout therefore contained irrigant fluid. To compensate for this additional dilution of any urothelial cells present, the results were expressed as the number of cells/μmol urinary creatinine.

All of the patients studied had indwelling catheters as part of their management and none had underlying pathology related to the urinary tract.

Bacteriology

The urine samples were inoculated on to MacConkey and 5% blood agar plates and incubated in air at 37°C for up to 48 h. Quantitative colony counts were then made. All positive isolates were identified using standard bacteriological techniques.

Microscopy

5 ml of each urine sample were added to an equal volume of 5% glutaraldehyde in 0.2 M sodium cacodylate buffer and centrifuged at 2000 rpm for 10 min: 9 ml of supernatant were removed and the sediments examined in a Fuch-Rosenthal counting chamber to determine the number of urothelial cells. Further aliquots of the sediment were examined after staining with crystal violet (Stennheimer and Malbin, 1951) and by the Papanicolaou (1947) technique.

Scanning electron microscopy

After fixation for up to 16h at 4°C in 5% glutaraldehyde, between 0.1 and 0.2 ml of the urine sediments were washed gently in 0.1 M sodium cacodylate buffer (pH 7.2) for 10 min. They were then sequentially dehydrated through an ethanol series followed by acetone at 10-min intervals. The cells were critically point dried (Polaron equipment) and gold coated for 2 min in a sputter coater (EM scope) as described by Elliott and Greenwood (1983). Electron micrographs were obtained using a Cambridge scanning electron microscope operated at an accelerating voltage of 20 kV.

Results

Normal control subjects exfoliated between 0 and 10 (average 8) urothelial cells/ml of urine and 0.93 cells/μmol of creatinine. The cells were predominantly single, with occasional pairs, and appeared to have an intact outline. The average urothelial exfoliation rate in the long-term catheterised patients who did not receive any washouts was 18 (range 0–72) cells/ml of urine. There did not appear to be any correlation between the exfoliation rate and the organism causing the chronic UTI. In comparison, patients in the prospective study had a similar urothelial exfoliation rate before the washout (average 16 cells/ml of urine) (Table). However, following consecutive bladder irrigations with either chlorhexidine or noxythiolin, there was a further significant increase in these patients' urothelial cell shedding (average 83.2 cells/ml of urine; $P<0.1$ Student's t test). There was no difference between the effect of the 2 irrigants. Similarly, in the cross-over study, patients exhibited an elevated urothelial rate of 2.6 cells/μmol of creatinine before the washout compared with the normal controls. After irrigation with either noxythiolin (Fig. 1A) or physiological saline (Fig. 1B), there was a further significant increase in exfoliation compared with the pre-irrigation level (saline $P<0.05$; noxythiolin $P<0.05$). No difference was found ($P<0.05$) between the urothelial shedding following irrigation with either saline or noxythiolin.

Table Urothelial Exfoliation Rates Following Consecutive Bladder Irrigations with either Chlorhexidine or Noxythiolin on 5 Patients with Long-term Indwelling Urinary Catheters and Chronic Urinary Tract Infections. Between each Bladder Washout there was a Period of at least 4 Days

			Urothelial cell exfoliation (cells/ml of urine)	
Patient no	*Irrigant*	*Washout number*	*Before washout*	*After washout*
1	Chlorhexidine	1	5	15
		2	5	370
		3	5	25
		4	0	120
2	Chlorhexidine	1	20	90
		2	24	54
		3	20	48
		4	24	98
		5	18	100
3	Noxythiolin	1	95	200
		2	20	50
		3	25	50
		4	0	120
4	Noxythiolin	1	5	20
		2	5	200
		3	10	94
		4	16	90
5	Noxythiolin	1	10	55
		2	20	45
		3	0	30
		4	0	40
		5	30	60
		6	25	48
Overall average			16	83 2

Statistical comparison between pre- and post-washouts $P < 0\ 1$

In both studies not only was there an increase in exfoliation following irrigation, but the shed cells also appeared grossly disrupted, with many in groups of up to 60 cells. The tight junctions between the cells in these clumps appeared intact (Fig. 2) but their surface topography was irregular and many lacked the microvillous structure present on fully differentiated bladder epithelial cells. There were also groups of cells present from the basal and intermediate urothelial layers.

All urine samples from both studies showed a significant bacteriuria ($>10^5$ organisms/ml of urine) prior to the irrigations. In the prospective study, all patients had an *Escherichia coli* UTI; in the cross-over study, 1 patient had a *Klebsiella* species and the remainder had a mixed growth of up to 6 different bacteria. These included *Proteus* species, *Streptococcus faecalis*, *Providencia stuartii*, *Enterobacter cloacae* and *Staphylococcus albus*. All urine samples contained a significant number (>5 white blood cells/high power field of view [×400]) of pus cells. The numbers of bacteria were largely unaffected by the irrigations, although in some cases there was a temporary reduction. On follow-up 2 weeks later, however, the same organisms were isolated from the urine of all patients.

Discussion

Long-term indwelling catheterisation and chronic urinary tract infections have been shown to be associated with bladder mucosal disruption (Ekelund and Johansson, 1979; Elliott *et al.*, 1985, 1986a). In a recent study we demonstrated that the exfoliation rate of bladder urothelial cells into the urine is a useful indicator of the severity of this mucosal damage (Elliott *et al.*, 1986b, 1987). The results obtained from the samples of control subjects and the pre-irrigation urines in the present investigation confirm that patients with long-term indwelling catheters and urinary infections show increased urothelial shedding and so demonstrate disruption of the bladder mucosa. In addition, it was indicated that further urothelial damage occurred during bladder irrigation as reflected by an increase in urothelial cell exfoliation. The presence of imma-

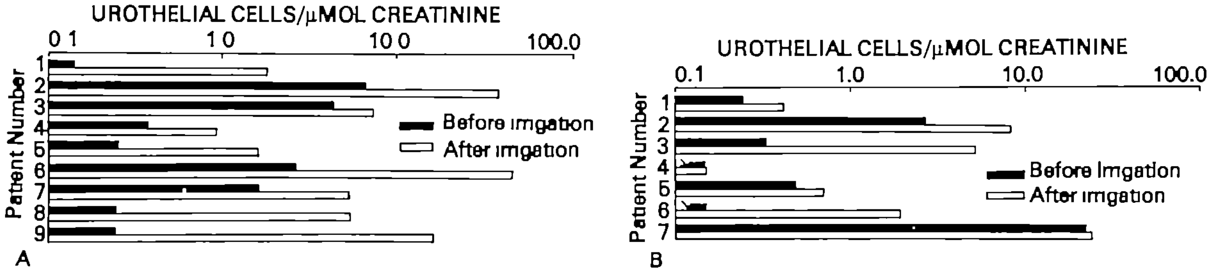

Fig. 1 The number of exfoliated urothelial cells in the urine of 9 long-term catheterised patients with chronic UTI, before and immediately following bladder irrigation with (A) 2 5% noxythiolin (9 patients) and (B) physiological saline (7 patients).

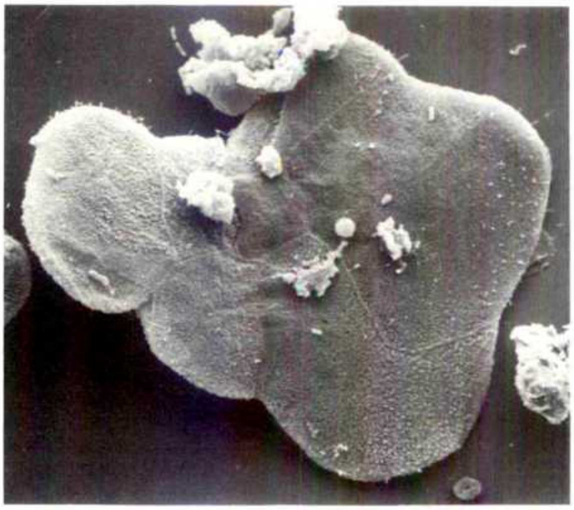

Fig. 2 Scanning electron micrograph of a group of exfoliated urothelial cells present in the urine of a long-term catheterised patient with a chronic *E. coli* UTI. A group of urothelial cells with intact tight junctions surrounded by cellular debris with occasional bacteria is shown. Bar length = 20 mμ.

ture epithelial cells in large sheets from the intermediate and basal layers following these washouts also demonstrated that the exfoliation was abnormal.

The increased exfoliation followed washouts with physiological saline, noxythiolin and chlorhexidine. Previous studies using animal models have demonstrated that various irrigants may result in erosive cystitis after contact for several hours with the bladder mucosa surface (Harper and Matz, 1975). Whilst this may conceivably have contributed to the present findings, particularly with the noxythiolin and chlorhexidine, the response to normal saline, and the rapidity of the resulting increase in exfoliation which occurred immediately after bladder irrigation, suggest that the physical forces of the irrigations resulted in removal of cell sheets from an already damaged urothelium. This would require confirmation by studying gravity fed bladder instillations. The increased exfoliation observed in this series, together with the failure of the washouts to eradicate infection, further suggest that bladder irrigation may not only be ineffective but also damaging. Bladder irrigation should only be performed in certain situations, such as blocked drainage systems, and in the light of these results their overall use requires reassessment.

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Biofilms, Bacteria and Bladder Catheters

A Clinical Study

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Summary—Biofilms were present on 16 of 33 urethral catheters examined. In 11 cases the catheter carried a different microbial flora from that of the bladder urine. The length of time the catheter was *in situ* did not influence biofilm formation, and all types of materials tested supported biofilm growth. Biofilms were seen on 2 of the 7 catheters where prophylactic antibiotics had been used.

Some species of micro-organisms are capable of growing both in a free form of liquid such as urine and also in the form of a biofilm adherent to a surface (Costerton, 1984). Once attached to the surface, the organisms produce a polysaccharide matrix or glycocalix which may protect them from the defence mechanisms of the host or from the action of antimicrobial agents (Gwynn *et al.*, 1981; Nickel *et al.*, 1985). Biofilms have been demonstrated on many commonly used medical prostheses (Gristina and Costerton, 1984; Ladd *et al.*, 1985; Costerton *et al.*, 1987). Multiple species of micro-organisms may combine in these biofilms, which may thus influence morbidity by increasing the incidence of symptomatic bacteriuria.

This study investigated the incidence and composition of biofilms on various indwelling urinary catheters, comparing the microorganisms present with those detected in bladder urine.

Patients and Methods

The study group comprised 33 patients (21 male, 12 female); 33 urethral catheters (25 siliconised latex, 3 solid silicone, 2 silicone elastomers, 2 PVC and 1 teflon-coated latex) were indwelling for 1 to 92 days (mode 2–3 weeks). Bladder urine and catheter surfaces were cultured and all organisms identified using antibiograms, API 20E (API Laboratory Products Ltd), and conventional bacteriological techniques (Cowan, 1974). Sections of catheters were examined for biofilm by direct fluorescent microscopy (using acridine orange staining) and by scanning electron microscopy.

Results

Biofilms were present on 16 of 33 catheters. Both the urine and catheter were sterile in 7 patients. Figures 1 and 2 illustrate the extent of bacterial growth on the catheter and show the condensed remains of the exopolysaccharide matrix.

In 11 catheters biofilm-associated organisms were seen which were different from those isolated from bladder urine (Table). In 6 cases the organisms were more numerous in the biofilm, in 2 cases no organisms at all were grown in the urine and in the remaining 3 cases species other than those in the synchronous bladder urine were isolated. Biofilms were seen in 2 cases but the catheter and the urine grew no organisms.

Discussion

The prophylactic use of antibiotics in catheterised patients has been extensively studied. Most authors

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Based on a Poster Demonstration at the 44th Annual Meeting of the British Association of Urological Surgeons in Buxton, June 1988

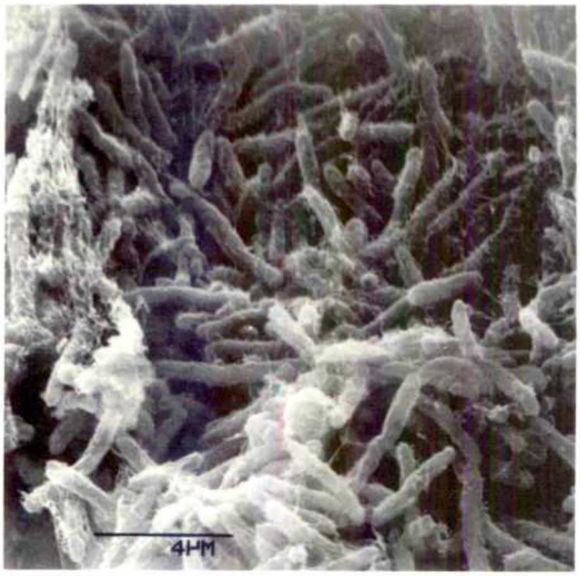

Fig. 1 *Proteus mirabilis* growing as a biofilm on siliconised latex. Note the evidence of a filamentous matrix surrounding the rods. This is probably condensed polysaccharide material.

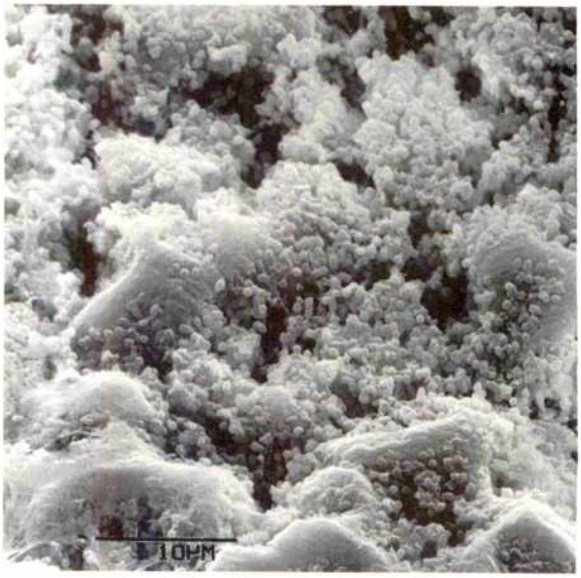

Fig. 2 Group D streptococci growing as a biofilm on siliconised latex. Extensive encasement in a fibrous matrix can be seen in the lower left hand quarter of the picture.

(Gonzalez *et al.*, 1976; Gibbons *et al.*, 1978; Mathew *et al.*, 1978; Millar *et al.*, 1987) reported a significant reduction in post-operative bacteriuria when antibiotics were used prophylactically prior to transurethral surgery. However, the significance of post-operative bacteriuria in terms of symptoms and prolongation of hospital stay is debatable (Hargreave *et al.*, 1982), especially when pre-operative cultures of urine are sterile (Hirschman and Inui, 1980; Millar *et al.*, 1987). When pre-operative bacteriuria is proven, septicaemia is a recognised complication of prostatic surgery (Sullivan *et al.*, 1973). In this situation, antibiotic prophylaxis can reduce the risk of this serious infection (Cafferkey *et al.*, 1982). However, in most of these studies septicaemia still occurred in some patients with apparently sterile urine pre-operatively and also in those who had received appropriate antibiotic therapy. These anomalies may be explained by the presence of organisms within a catheter biofilm which do not appear in bladder urine. When bacteriuria is present, the organisms isolated from bladder urine may not be representative of the biofilm flora.

This study confirmed that biofilms were present in 48.5% of those catheters examined. In a proportion of cases (2 of 7), biofilms were seen even in the presence of prophylactic antibiotics. Furthermore, the isolation of organisms in the biofilm which were different from those in the bladder urine suggests that antibacterial prophylaxis based on the culture of bladder urine alone might have been ineffective in these patients.

Urethral catheters are manufactured in a variety of materials but all of those examined in this study supported the growth of biofilms. We did not seek to address the problem of catheter encrustation. Previous studies have related urinary tract infection to encrustation and have shown silicone biomaterials to be superior to other polymers (Binder and Gonick, 1969). Experimental studies comparing silicone and hydrogel (Cox *et al.*, 1988), silicone, PVC nylon and hydrogel (Crocker *et al.*, 1986; Ramsay *et al.*, 1986) and clinical studies of upper urinary tract prostheses (Ramsay *et al.*, 1987) have suggested that polymer surface morphology and the presence of certain microorganisms were not the only determinants of biomaterial encrustation. Further studies are in progress to determine the role of polymer morphology in bacterial adherence and the relationship between biofilms, bacteria and biomaterial encrustation.

Table Organisms Grown in Urine and on Biofilm. Their Relationship to Catheter Material, Duration *in situ* and Use of Antibiotics

No	*Urine*	*Catheter*	*Material*	*Biofilm*	*In situ (days)*	*Antibiotic*
1	*St. epidermidis* *St simulans*	NG	L	−	35	—
2	NG	NG	L	+	14	Ceph
3	Chromobacterium	*P. morgani* *K pneumoniae*	L	−	35	—
4	NG	NG	L	−	4	Amp
5	NG	NG	L	−	1	Gent
6	NG	NG	L	−	16	—
7	*St epidermidis*	*St epidermidis*	L	−	7	—
8	*E. coli*	NG	L	+	12	Gent
9	NG	*Ps. fluorescens* *E coli*	PVC	+	14	—
10	*E coli*	*E. coli* *P. mirabilis* *Ps fluorescens* Strep. Gp. D	SE	−	7	—
11	Diphtheroids	Diphtheroids	SE	+	7	—
12	*P. mirabilis* *E. coli*	*P mirabilis* Strep. Gp. D	L	−	40	Trim
13	*E coli* *K pneumoniae*	*K oxytoca* Enterobacteria	L	−	49	—
14	Non ferm. Gm-ve	Non ferm G-ve	SS	−	84	—
15	Strep. Gp. D	Strep. Gp D	SS	−	31	—
16	*E. coli*	*E. coli* Non ferm G-ve	L	−	14	Amp
17	*K oxytoca* *Citrobacter* spp	*K oxytoca* *Citrobacter* spp.	L	+	92	—
18	*Prov stuartii*	*Prov. stuartii*	L	+	21	—
19	*Prov stuartii*	*Prov stuartii* *K. oxytoca* Strep Gp G	L	+	28	—
20	*P mirabilis* Strep. Gp C	*Prov stuartii* Strep. Gp. D	L	+	21	—
21	*P. mirabilis*	*P mirabilis* *E coli*	L	−	21	—
22	*Prov stuartii* *E. coli*	*Prov. stuartii* *E coli*	L	+	35	—
23	*P mirabilis*	*P mirabilis* *Ps aeruginosa*	SS	+	21	—
24	*Ps aeruginosa*	*Ps aeruginosa*	L	+	42	—
25	*Candida* spp.	*Candida* spp	L	−	16	Netilmicin
26	NG	*Staph epidermidis*	L	−	1	—
27	Strep Gp D	Strep. Gp D	L	+	8	—
28	*K pneumoniae*	*K pneumoniae*	Teflon	+	14	—
29	*P. mirabilis* Strep. Gp. B	*P mirabilis* Strep Gp. B	L	+	10	—
30	NG	NG	PVC	−	8	—
31	NG	NG	L	+	3	—
32	*Ent cloacae* *Ps. aeruginosa*	*Ent cloacae* *Ps. aeruginosa*	L	+	21	—
33	NG	NG	L	−	7	—

NG = No growth, L = Latex, SE = Silicone elastomer, PVC = Polyvinyl chloride, SS = Solid silicone, Teflon = Teflon coated latex, Amp = Ampicillin, Gent = Gentamicin, Ceph = Cephalosporin, Trim = Trimethoprim

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Bladder Tumours in Enugu, Nigeria

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Summary—The clinicopathological features of 103 tumours of the urinary bladder are reported; 56.3% were transitional cell and 38.8% were squamous cell carcinoma. The results support a strong association between schistosomiasis and bladder cancer.

The pattern and management of disease vary from one geographical area to another and bladder cancer in Africans has been extensively reported (Prates, 1962; von Lichtenberg *et al.*, 1971; El-Sebai, 1981; Lucas, 1982; Garg *et al.*, 1984; Al-Shukri *et al.*, 1987).

Patients and Methods

The records were reviewed of all patients (n = 103) with histologically diagnosed bladder tumours seen at the University of Nigeria Teaching Hospital between January 1974 and December 1986. Age, sex, presentation, investigations and treatment were analysed. The age distribution is shown in Table 1. Most patients (75.7%) presented between the ages of 30 and 59 years (mean 46.3).

A summary of their clinical presentation is outlined in Table 2. A history of schistosomiasis was elicited in 18 patients and a significant number presented with advanced disease. Group A comprised 63 patients who presented within 6 months of the onset of symptoms and 52 of these were in the upper social class. Group B included 40 patients who presented 7 to 15 months after the onset of symptoms (Table 3) and all were of low social status. Staging of the tumour was done in 100 cases and 52% were found to have advanced disease.

Table 1 Age Distribution

Age (years)	*Males*	*Females*	*Total*
10–19	2	0	2
20–29	12	0	12
30–39	18	4	22
40–49	25	6	31
50–59	15	10	25
60–69	3	4	7
70–79	2	2	4

Table 2 Clinical Presentation

Presentation	*No. of patients*
Haematuria	89
Weight loss	77
Severe anaemia	59
Dysuria	26
Acute urinary retention	23
Suprapubic mass (without urinary retention)	20
Past history of schistosomiasis	18
Passage of whitish specks	12
Urinary frequency	8
Secondaries in other parts of the body	4
Poor urinary stream	3
Incontinence	2

Table 3 Duration of Symptoms Before Presentation

Duration (months)	*No. of patients*
0–1	14
1–2	14
2–3	10
3–4	10
4–5	3
5–6	12
6–7	—
7–8	6
8–9	2
9–10	—
10–11	—
11–12	14
12–13	6
13–14	7
14–15	5

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Three patients (2 with leiomyosarcoma and 1 with leiomyoma) were excluded (Table 4). Intravenous urography was carried out in 89 patients, 80 of whom had a filling defect in the bladder (Fig.). The ratio of papillary to solid tumours (determined by cystoscopy or cystotomy) was equal (Table 5). The right lateral wall was the most frequently involved.

The histology is presented in Table 6. Transitional cell carcinoma was the commonest (56.3%); 40 patients (38.8%) had squamous cell carcinoma, of whom 36 came from an endemic area for schistosomiasis, though only 17 gave a history of schistosomiasis; 82.8% of patients with transitional cell carcinoma were in the upper social class compared with 5% of those with squamous cell carcinoma; 24% of the patients with transitional cell carcinoma came from endemic areas of schistosomiasis.

The various treatments are shown in Table 7. Four patients were admitted in a very poor clinical state. They were managed with analgesics only and blood transfusion and all died in hospital.

Results

The results of treatment are shown in Table 8. All of the patients with T4 tumours died within 2 years of diagnosis and only 6 of the 52 with T2–T3 tumours lived for more than 2 years after diagnosis. The patient with leiomyosarcoma was lost to follow-up and the patient with leiomyoma was discharged, free of recurrence, after 5 years' follow-up.

Table 4 Tumour Stage

Stage	*No. of patients*
T1	16
T2–T3	52
T4	32

Table 5 Findings at Cystoscopy/Open Cystotomy

Type of growth	*No. of patients*
Solid	45
Papillary	46
Mixed	12

Table 6 Histology

Type	*No. of patients*
Transitional cell Carcinoma	58
Squamous cell Carcinoma	40
Adenocarcinoma	2
Leiomyosarcoma	2
Leiomyoma	1

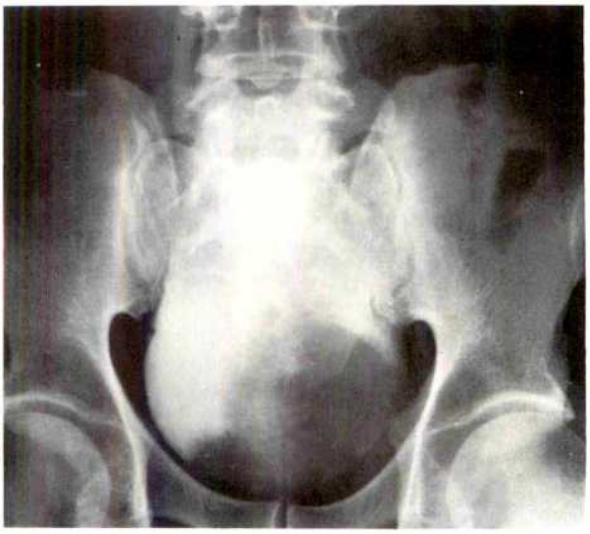

Fig. Huge, irregular filling defect in the base and left lateral wall of the bladder.

Table 7 Treatment

Treatment	*No. of patients*
Open excision plus fulguration ± intravesical or systemic chemotherapy	55
Transurethral resection or cystoscopic fulguration ± intravesical or systemic chemotheraphy	28
Total cystectomy ± bilateral ureterosigmoidostomy	8
Radiotherapy	4
Partial cystectomy	4
No definitive treatment (palliative management)	4

Table 8 Results of Treatment

	T1	*T2–T3*	*T4*	*Total*
Total	16	52	32	100
Died in hospital	0	0	4	4
Discharged and lost to follow-up	4	21	21	46
Died or lost to follow-up, up to 1 year	2	15	5	22
Died or lost to follow-up between 1 and 2 years	3	10	2	15
Alive more than 2 years	7	6	—	13

Discussion

The mean age at presentation was 46.3 years in the present study. This compared with mean ages of 44.9 years in Malawi (Lucas, 1982), 45 in Kuwait (Al-Shukri *et al.*, 1987) and 43 in Zaria, Nigeria (Garg *et al.*, 1984).

The strong relationship between schistosomiasis and squamous cell carcinoma of the bladder is supported by the evidence that 94.4% of patients with a history of schistosomiasis had squamous cell carcinoma; 90% of all cases of squamous cell carcinoma came from endemic areas of schistosomiasis (Lucas, 1982; Garg *et al.*, 1984; Al-Shukri *et al.*, 1987). Only 24% of patients with transitional cell carcinoma came from endemic areas. Oyasu and Hopp (1974) have studied the possible mechanism of action.

The social class of patients influenced the time of presentation, most of those who presented late being illiterate individuals who had seen traditional healers before coming to hospital.

The "white line sign" seen of IVU was valuable in the diagnosis of bladder cancer (Simpson *et al.*, 1974). Ultrasonography and CT scans were not available to us.

The right lateral wall was the commonest site found in this and other studies (Melicow, 1974). Our incidence of 38.8% for squamous cell carcinoma is low compared with that reported in other African studies: Lucas (1982) reported 80.1% from Malawi and Garg *et al.* (1984) reported 70% from Zaria, Nigeria. Reports from Kuwait and the Middle East showed a higher incidence of squamous cell carcinoma (Al-Shukri *et al.*, 1987). We believe that social status, geographical location and occupation played a part in determining the histological type. Transitional cell carcinoma was usually found amongst members of the upper social class, who live in urban areas and may be exposed to urogenous carcinogens, whereas squamous cell carcinoma is commoner in the low social classes, mainly farmers who are more likely to be exposed to infestation with schistosomiasis.

Most patients encountered in the early phase of this study had open resection and fulguration as the primary treatment. When endoscopic facilities and expertise became available, many underwent endoscopic resection.

Intravesical chemotherapeutic agents used included thiotepa, Epodyl, Adriamycin and mitomycin C. The responses to local treatment were not dramatic and we were particularly concerned about chemical cystitis with Adriamycin treatment. It has been suggested that the incidence and severity of chemical cystitis could be reduced by selecting patients with no other forms of cystitis and avoiding an early start of treatment (Pavone-Macaluso *et al.*, 1984; Powell and Williams, 1984; Smith, 1984).

Systemic chemotherapeutic agents employed were methotrexate, cyclophosphamide, Adriamycin and 5-fluorouracil either alone or in combination. The results of adjuvant chemotherapy in this study were disappointing. There are reports in the literature of the usefulness of methotrexate given in cycles (Hall, 1984), although the relapse rates were high. Richards *et al.* (1983) and Clyne *et al.* (1983) have shown that a combination of Adriamycin and 5-fluorouracil decreases morbidity with no change in mortality as compared with a control group.

The survival rate for the patients in our study cannot be given accurately since their poverty and ignorance make follow-up almost impossible. Many patients, once told the nature of their illness and the need for follow-up, prefer to go to spiritual and traditional healers either because they cannot afford continued treatment or because they lose confidence in hospital treatment, where an immediate cure cannot be guaranteed. Of the 96 patients who were discharged from hospital, 46 did not attend the follow-up clinic. Apart from the 13 patients who were followed up for more than 2 years, it was not possible to account for the rest, since only 5 deaths were reported to the hospital. It is hoped that with better education and improved diagnostic techniques and therapeutic facilities, the morbidity and mortality rates will fall.

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DNA Ploidy and the Prognosis of Stage pT1 Bladder Cancer

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Summary—The histopathological grade, proportion of "S"-phase nuclei and DNA ploidy values were linked and of prognostic significance in a retrospective series of stage pT1 bladder cancers. Nuclei were extracted from paraffin sections of 75 biopsies (56 patients). DNA ploidy and the proportion of "S"-phase nuclei were measured using flow cytometry. Progressive disease (pT2 or greater) developed within 3 years in 35% (6/17) of patients with poorly differentiated tumours, 35% (8/23) with aneuploid tumours and 35% (7/20) of those with a high proportion of "S"-phase nuclei. Of 8 tumours with all 3 features, progressive disease developed in 6 cases (75%). Of 9 patients who developed progressive disease, 8 (89%) had aneuploid tumours. Progressive disease did not develop in 11 patients with well differentiated tumours, compared with 4% (1/24) in diploid/tetraploid tumours and 7% (2/27) in those with a low/medium percentage of "S"-phase nuclei. In contrast to muscle-invasive disease, recurrent superficial tumours developed with a high incidence in all groups. Only 6/56 patients (11%) remained alive and disease-free for 3 years. It is concluded that these 3 features are of similar prognostic significance and accuracy in identifying patients requiring more aggressive therapy.

Superficial (stage pTa and pT1) transitional cell carcinomas of the bladder recur in approximately 70% of patients and 10 to 20% develop muscle-invasive disease (stage pT2 or greater). An accurate method for predicting which patients will develop progressive disease would have a major impact on the management of superficial bladder cancer.

DNA ploidy is associated with the histopathological grade (Tribukait *et al.*, 1982; Farsund *et al.*, 1984; Gustafson and Tribukait, 1985; Coon *et al.*, 1986) and prognosis (Tavares *et al.*, 1966; Frankfurt and Huben, 1984; Fossa and Kaalhus, 1985; Murphy *et al.*, 1986; Oljans and Tanke, 1986; Blomjous *et al.*, 1988; deVere White *et al.*, 1988) of bladder cancer.

The histogram obtained by plotting DNA ploidy values also permits an approximate estimate of the fraction of cells in each phase of the cell cycle. The percentage of cells in S-phase (those synthesising DNA) provides an index associated with the rate of proliferation of the tumour. High proportions of "S"-phase nuclei in bladder cancers are associated both with increased stage (Tribukait, 1982) and poor differentiation (Farsund *et al.*, 1984).

The clinical value of DNA ploidy as a prognostic index for superficial bladder cancer is debatable for 2 reasons. Firstly, many of the published studies do not separate the prognostic significance of DNA ploidy and stage of disease. Secondly, some studies have analysed tumours of selected histopathological grades. In contrast, this study used an unselected series of bladder cancers at 1 stage of disease and provided data with which to determine the relative values of histopathological grade, DNA ploidy and the proportion of "S"-phase nuclei.

Patients and Methods

All patients with transitional cell carcinoma of the bladder presenting in 1978 and 1979 and fulfilling

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the following 3 criteria were included in the study: (1) a diagnosis of stage pT1 disease, (2) a minimum of 3 years' follow-up and (3) no previous treatment other than local therapy. All patients were followed by routine cytoscopic evaluation as well as transurethral treatment where appropriate; 13 were excluded because the follow-up was inadequate. There were 77 biopsies from 56 patients (53 male), 43 of whom provided 1 specimen and 13 provided 2 to 4 specimens over the 2-year period. Thirty patients had primary tumours and 26 had recurrent disease. The age range was 42 to 82 years (mean 66).

Pathological staging was assessed routinely by experienced pathologists, who also subdivided these tumours into Pla and Plb disease, a refinement of the UICC staging system (Pugh, 1973; UICC, 1978). The original haematoxylin and eosin stained sections were graded by one pathologist using the WHO classification of well (grade 1), moderately (grade 2) and poorly (grade 3) differentiated tumours (WHO, 1973).

DNA ploidy values and an estimate of the proportion of "S"-phase cells were obtained using nuclei extracted from 40 μ sections cut from paraffin-embedded tissue, as previously described (Camplejohn and Macartney, 1985; Masters *et al.*, 1987). In summary, the nuclei were extracted with pepsin and stained with DAPI before filtration to remove clumps. A minimum of 10,000 nuclei from each sample were processed using a Becton Dickinson FACS Analyser. The DNA index was calculated by measuring the position of any aneuploid G1 peak relative to the normal GO/G1 peak. Tumours with a ratio of 1.0 were classified as diploid, 1.9 or 2.0 as tetraploid and the remainder as aneuploid. In diploid tumours the "S"-phase fraction was calculated according to the method of Baisch *et al.* (1975). For aneuploid tumours we estimated the total number of aneuploid cells and used the Baisch method to calculate the aneuploid "S"-phase fraction as a percentage of the total number of aneuploid cells. The "S"-phase fraction was classified as low (0-7%), medium (>7-14%) or high (>14%).

Results

The first biopsy obtained from each patient was used for the data analysis. The 56 biopsies were classified according to pathological substage into 18 Pla (32%) and 38 Plb (68%) tumours, and by histopathological grade into 11 G1 (20%), 28 G2 (50%) and 17 G3 (30%) tumours. DNA ploidy was measurable in 47 (84%) of these biopsies. Nine cases were excluded because the number of nuclei was inadequate or the CV (a measure of the breadth of the cell cycle phase G1 peak and thus the quality of the sample) was excessive (>5.5). The CVs ranged from 2.6 to 5.5 (mean 4.2). These 47 biopsies were classified into 13 diploid (28%), 11 tetraploid (23%) and 23 aneuploid (49%). According to the proportion of "S"-phase nuclei the tumours were classified as 14 low (30%), 13 medium (28%) and 20 high (43%).

The relationships between flow cytometry measurements and histopathological features are shown in Table 1. Diploid and tetraploid tumours tended to present at the lower (Pla) stage and were frequently either well or moderately differentiated ($P<0.05$) with fewer "S"-phase nuclei ($P<0.05$). None of the diploid tumours was poorly differentiated.

The associations between the proportions of "S"-

Table 1 Diploid, Tetraploid and Aneuploid Tumours, Subdivided according to Pathological Substage (Pla or Plb), Grade (1, 2 or 3) and Proportion of "S"-phase Nuclei (low, medium or high)

	Diploid (n=13) (%)	*Tetraploid (n=11) (%)*	*Aneuploid (n=23) (%)*
Substage			
Pla (16)	7 (44)	4 (25)	5 (31)
Plb (31)	6 (19)	7 (23)	18 (58)
Grade			
1 (Well differentiated) (11)	9 (82)	1 (9)	1 (9)
2 (Moderately differentiated) (21)	4 (19)	6 (29)	11 (52)
3 (Poorly differentiated) (15)	0 (0)	4 (27)	11 (73)
Proportion of "s-phase" nuclei			
Low (14)	12 (86)	0 (0)	2 (14)
Medium (13)	1 (8)	5 (38)	7 (54)
High (20)	0 (0)	6 (30)	14 (70)

phase nuclei and the histopathological features are shown in Table 2. Tumours with a high proportion of "S"-phase nuclei were more likely to be poorly differentiated ($P<0.01$) but showed no significant association with the more advanced pathological substage, Plb.

DNA ploidy could be evaluated in more than 1 biopsy from 13 patients. In 8 cases up to 4 biopsies were all aneuploid, but in 5 (38%) DNA ploidy classification changed between biopsies. Three patients appeared to progress—1 diploid tumour became tetraploid, and 1 diploid and 1 tetraploid tumour became aneuploid. In contrast, the other 2 patients apparently became better differentiated—1 aneuploid and 1 tetraploid tumour showed diploid recurrences. Two of these 5 patients received treatment between the cystoscopies—1 whose tumour reverted from aneuploid to diploid received systemic cisplatin and methotrexate, the other, whose tumour went in the reverse direction, received intravesical mitomycin-c.

There were no significant differences amongst the distributions of the variables studied between primary and recurrent tumours (Table 3). The 56 patients evaluated had between 3 and 8 year's follow-up, and all but 4 were followed up for at least 5 years. The relationships between the variables studied and clinical outcome at 3 years are shown in Table 4.

Of the 56 patients, 10 (18%) developed progressive disease (pT2 or greater) which proved fatal in 6 cases (11%); 31 patients (55%) developed superficial (Pa or Pl) recurrences, 6 (11%) were disease-free and 9 (16%) died of other causes within the 3-year follow-up period. Development of progressive disease was associated with the more advanced

Table 2 Tumours with Low, Medium and High Proportions of "S"-phase Nuclei, Subdivided according to Substage (Pla or Plb) and Grade (1, 2 or 3)

	Proportion of "S"-phase nuclei		
	Low (n=14) (%)	*Medium (n=13) (%)*	*High (n=20) (%)*
Substage			
Pla (16)	6 (38)	3 (19)	7 (44)
Plb (31)	8 (26)	10 (32)	13 (42)
Grade			
1 (Well differentiated) (11)	9 (82)	2 (18)	0 (0)
2 (Moderately differentiated) (21)	4 (19)	8 (38)	9 (43)
3 (Poorly differentiated) (15)	1 (7)	3 (20)	11 (73)

Table 3 Relationship between Status (Primary or Recurrent) of First Biopsy Studied and Substage, Grade, DNA Ploidy and Proportion of "S"-phase Nuclei

	Primary (n=30) (%)	*Recurrent (n=26) (%)*
Substage		
Pla (18)	10 (56)	8 (44)
Plb (38)	20 (53)	18 (47)
Grade		
1 (Well differentiated) (11)	5 (45)	6 (55)
2 (Moderately differentiated) (28)	13 (46)	15 (54)
3 (Poorly differentiated (17)	12 (71)	5 (29)
DNA Ploidy		
Diploid (13)	6 (46)	7 (54)
Tetraploid (11)	7 (64)	4 (36)
Aneuploid (23)	14 (61)	9 (39)
Proportion of "S"-phase nuclei		
Low (14)	5 (36)	9 (64)
Moderate (13)	7 (54)	6 (46)
High (20)	15 (75)	5 (25)

Table 4 Clinical Status at 3 Years in Relation to Pathological Substage, Grade, Tumour Status (Primary or Recurrent), DNA Ploidy, Proportion of "S"-phase Nuclei and DNA Ploidy in Grade 2 Tumours. (Numbers in parenthesis below each classification indicate the numbers of tumours in this category. The numbers of patients dead of disease are indicated in parenthesis underneath the numbers developing progressive disease; pT2 or greater)

	Substage		*Tumour status*		*Histological grade*		
	Pla (n=18) (%)	*Plb (n=38) (%)*	*Primary (n=30) (%)*	*recurrent (n=26) (%)*	*Well 1 (n=11) (%)*	*Moderate 2 (n=28) (%)*	*Poor 3 (n=17((%)*
Disease-free (6)	3 (17)	3 (8)	6 (20)	0 (0)	1 (9)	4 (14)	1 (6)
Superficial recurrence (31)	12 (67)	19 (50)	14 (47)	17 (65)	9 (82)	16 (57)	6 (35)
Invasive recurrence (10)	1 (6)	9 (24)	4 (13)	6 (23)	0 (0)	4 (14)	6 (35)
(dead of disease)	(1)	(5)	(1)	(5)		(2)	(4)
Dead other cause (9)	2 (11)	7 (18)	6 (20)	3 (12)	1 (9)	4 (14)	4 (24)

	DNA Ploidy			*Proportion of "S"-phase nuclei*		
	Diploid (n=13) (%)	*Tetraploid (n=11) (%)*	*Aneuploid (n=23) (%)*	*Low (n=14) (%)*	*Medium (n=13) (%)*	*High (n=20) (%)*
Disease-free (6)	2 (15)	2 (18)	2 (9)	2 (14)	0 (0)	4 20
Superficial recurrence (25)	9 (69)	7 (64)	9 (39)	8 (57)	10 (77)	7 (35)
Invasive recurrence (9)	1 (8)	0 (0)	8 (35)	1 (7)	1 (8)	7 (35)
(dead of disease)	(1)		(5)	(1)	(1)	(3)
Dead other cause (7)	1 (8)	2 (18)	4 (17)	3 (21)	2 (15)	2 (10)

	Grade 2 Tumours		
	Diploid (n=4) (%)	*Tetraploid (n=6) (%)*	*Aneuploid (n=11) (%)*
Disease-free (4)	1 (25)	1 (17)	2 (18)
Superficial recurrence (11)	2 (50)	4 (67)	5 (45)
Invasive recurrence (3)	1 (25)	0 (0)	2 (18)
(dead of disease)	(1)		(1)
Dead other cause (3)	0 (0)	1 (17)	2 (18)

substage (Plb), recurrent superficial disease, poor differentiation, aneuploidy and a high proportion of "S"-phase nuclei. Eight patients had tumours combining the features of poor differentiation, aneuploidy and a high proportion of "S"- phase nuclei; 6 of these (75%) developed progressive disease and 4 died as a result within 3 years. In only 1 group did progressive disease not develop— those patients with well differentiated tumours. Only 6/56 patients remained alive and disease-free at 3 years, and these were distributed equally amongst the various groups.

The moderately differentiated tumours were divided according to their DNA ploidy status (Table 4), but this combination did not appear to provide an improved separation of prognostic groups.

It has been suggested that bladder tumours with a ploidy value >1.5 are more likely to recur than those with a value equal to, or less, than 1.5 (Oljans and Tanke, 1986). In the present study, of 17 patients with tumours whose DNA ploidy values were <1.5, 3 developed progressive disease, 9 developed superficial recurrences, 4 were clear of disease and 1 died of other causes during the 3-year follow-up period. Of the 30 patients with ploidy values >1.5, 6 developed progressive disease, 16 developed superficial recurrences, 2 were clear of disease and 6 died of other causes. These data do not indicate that bladder tumours of different prognostic groups can be separated using ploidy values greater and lesser than 1.5.

Tribukait (1984) showed that aneuploid tumours with a multiple stemline (*i.e.* more than 1 aneuploid peak on the DNA histogram) have a poor prognosis. In the present study, 5/23 aneuploid tumours (22%)

had a multiple stemline. Two of these patients (40%) developed progressive disease during the 3-year follow-up period, compared with 6/18 (33%) of those with a single stemline.

Discussion

The prognostic significance of DNA ploidy values, histopathological grade and proportion of "S"-phase nuclei was assessed in an unselected retrospective series of pT1 bladder tumours with a minimum of 3 years' follow-up. The 3 features are strongly associated and each provides information of similar prognostic significance.

Tumour grade provides prognostic information already used in patient management. None of the patients with well differentiated tumours developed progressive disease (pT2 or greater), whereas nearly 35% of those with poorly differentiated tumours developed muscle-invasive disease within 3 years. These data provide further support for the concept that P1G3 tumours require treatment in addition to regular cystoscopic review (Jakse *et al.*, 1987).

DNA ploidy also provides prognostic information. Of the patients with diploid and tetraploid tumours only 4% developed more advanced disease, compared with 35% of those with aneuploid tumours. Similarly, the proportion of "S"-phase nuclei is related to clinical outcome. Of patients with tumours containing a low or moderate proportion of "S"-phase nuclei, 7% developed progressive disease, compared with 35% of those with a high proportion.

It has been suggested that bladder tumours progress from diploid to aneuploid through an intermediate tetraploid stage (Devonec *et al.*, 1986). The results from this study support this hypothesis to the extent that tetraploid tumours were intermediate in terms of substage (P1a or P1b) and grade. However, in terms of clinical outcome, patients with tetraploid tumours had a similar prognosis to those with diploid tumours. Thus DNA ploidy could be classified in 2 groups, aneuploid and diploid/tetraploid, for the purpose of predicting clinical outcome.

Table 5 Sensitivities and Predictive Values of Grade 3, Aneuploidy and High "S"-phase Fraction for Selecting Patients who will Develop Progressive Disease (pT2 or greater) (Sensitivity is defined as the number of patients with progressive disease and the prognostic factor as a proportion of the number of patients with progressive disease. Predictive value is defined as the number of patients with progressive disease and the prognostic factor as a proportion of the number of patients with the prognostic factor)

	Sensitivity (%)	*Predictive value (%)*
Grade 3	6/10 (60)	6/17 (35)
Aneuploidy	8/9 (89)	8/23 (35)
High "S"-phase fraction	7/9 (78)	7/20 (35)

The sensitivities and predictive values of using either high grade, aneuploidy or high "S"-phase fraction to select those patients who will develop muscle-invasive disease are summarised in Table 5. Comparing the values of these features as prognostic indices, a number of factors must be considered. Measurement of DNA ploidy requires expensive equipment and expert technical support. Histopathological grading of bladder tumours also has limitations. Firstly, it is subjective and reproducibility between pathologists is poor. In this study all tumours were graded over a short period of time by an experienced histopathologist, and therefore the data provided more accurate prognostic information than would be achieved in routine assessments. Secondly, in this study half of the tumours were G2, and this classification provides little additional information on which to base clinical management. It has been suggested that the measurement of DNA ploidy in G2 tumours differentiates these into good and bad prognosis (Oljan and Tanke, 1986; Blomjous *et al.*, 1988); together with Murphy *et al.* (1986), however, we failed to confirm these findings.

Blomjous *et al.* (1988) found that only patients with aneuploid superficial tumours developed progressive disease, which contrasts with both this study and that of Murphy *et al.* (1986). However, more advanced tumours (pT2 or greater) are not necessarily aneuploid. For example, in the study by Fossa and Kaalhus (1985), 20/60 (33%) of T2-T4 tumours were diploid, and Blomjous *et al.* (1988) reported that 4/24 (17%) were diploid and a further 6/24 (25%) peritetraploid. In a study of TaG1 and TaG2 disease, 3/4 of the tumours that became progressive were diploid (deVere White *et al.*, 1988). Nevertheless, aneuploidy does have a high sensitivity for predicting which tumours will progress; in the present study 8/9 (89%) of the patients who developed muscle-invasive disease had aneuploid pT1 tumours.

DNA ploidy status and grade can change between primary and recurrent tumours as well as between recurrences. We found that DNA ploidy status changed in 5/13 cases (38%). Similarly, Tribukait (1987) found that 16% of 51 aneuploid primary tumours became diploid at recurrence and 21% of 90 initially diploid tumours became aneuploid over a 2.6-year follow-up period. These data indicate that whichever prognostic feature is selected, the assessment must be repeated for each recurrence.

Prognostic information selecting 2 other groups of patients, those developing superficial recurrences and those that never recur, would also aid clinical management. None of the features in this study was of any value in identifying either of these groups.

In conclusion, DNA ploidy values and "S"-phase fractions provide prognostic information of clinical significance similar to that of histopathological grade. In the routine setting, each of the 3 features gives percentage information concerning prognosis and leaves ample scope for clinical judgement.

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Detection of Recurrent Bladder Tumours by Transrectal and Abdominal Ultrasound Compared with Cystoscopy

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Summary—Transrectal and transabdominal ultrasound was used to detect the recurrence of bladder tumours and compared with conventional cystoscopy. Forty patients with a previous history of bladder tumour were examined by these methods; 50% had a recurrence.

Transabdominal and transrectal ultrasound together identified 95% of recurrences; 1 tumour (diameter 1 mm) was missed. The false positive rate was 5% and these areas, identified wrongly by ultrasound as tumour, were shown to be scars on cystoscopy. Combination ultrasound may be used as an alternative to check cystoscopy in certain categories of bladder tumour.

The follow-up of patients with transitional cell carcinoma of the bladder takes up a considerable amount of time in a general urological practice. Recurrence rates of 50–70% are seen in patients with non-invasive tumour (Miller *et al.*, 1969). As a result of these high recurrence rates, cystoscopy becomes a repetitive procedure performed on elderly patients who are not ideal candidates for general anaesthesia. Apart from this, the financial aspect of recurrent admissions is not inconsiderable. Thus it would be advantageous to find an effective, non-invasive alternative. Various non-invasive methods have been used to follow up these patients, including abdominal ultrasound and cytology (Juul *et al.*, 1986; Malone *et al.*, 1986), history, urine analysis and cytology (Meuleman and Delaere, 1988). Transabdominal ultrasound has given tumour detection rates of 50, 74 and 77% in the studies performed by Malone *et al.* (1986), Vallancien *et al.* (1986) and Juul *et al.* (1986) respectively.

In this study we compared the detection of recurrent tumour by the use of transabdominal ultrasound, transrectal ultrasound and cytology with cystoscopy alone.

Patients and Methods

Forty patients (30 male and 10 female) with a mean age of 60 years (range 39–78) were admitted for day-case check cystoscopy at a mean time since diagnosis of 26 months (range 3–237). The ultrasound examinations were performed in theatre at the same time as the cystoscopy using a Bruel and Kjaer ultrasound machine (Type 1846) with a 4 MHz abdominal probe and a 7 MHz transrectal probe giving longitudinal scans. The cystoscopy was performed first, urine sent for cytology, the bladder filled, and then the ultrasound examinations were performed by 1 of 2 surgeons who had no previous ultrasound experience and a radiology registrar. At the time of the examination the cystoscopy findings of the previous follow-up were known. Each examination was conducted by a different person who was unaware of the results of the other investigations.

Results

Table 1 shows the results of the ultrasound examinations compared with those of cystoscopy. Abdominal and transrectal ultrasound had a detection rate of 80 and 85% respectively. In combination, the ultrasound technique detected 95% of tumours; the tumour missed was 1 mm in diameter.

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Table 1 Comparison of Ultrasound with Cystoscopy for Tumour Identification

Cystoscopy	*Abdominal ultrasound*	*Transrectal ultrasound*	*Combination ultrasound*	*Clear*
20	16	17	19	20
F +ve	1	2	2	

Table 2 Site of Tumours

Site	*No.*
Base	5
Anterior	2
Vault	2
Right lateral wall	8
Left lateral wall	16

Table 3 Size of Largest Tumour in 20 Patients with Recurrence

Size (mm)	*No.*
>10	2
6–10	5
2–5	12
<2	1

In this patient the cytology was positive. On ultrasound examination there were only 2 false positives; the areas identified were the sites of a scar from a previous resection.

Cytology detected 80% of patients with recurrent tumour. In 15% the cytology report was equivocal and in 1 case (5%) a tumour was missed. If the results of combination ultrasound and cytology are summated, the sensitivity of this method compared with cystoscopy was 100%.

Table 2 illustrates the location of the 33 tumours, the majority (73%) being on the lateral walls. Table 3 shows the diameter of the largest tumour in the 20 patients as measured at the time of cystoscopy.

The Figure shows tumour recurrences using transabdominal and transrectal scans.

Discussion

The results show that a combination of transabdominal and transrectal ultrasound can be used to detect bladder recurrence with a high degree of diagnostic accuracy. To our knowledge, the use of transrectal ultrasound for this purpose has not been previously described. The accuracy rates with cytology range from 72 to 98% (Sutton *et al.*, 1979; Meuleman and Delaere, 1988). A combination of transabdominal and transrectal ultrasound produced better detection rates than those reported by other workers (Table 4). Furthermore, in 60% of patients in this study the tumours measured 2 to 5 mm, sizes which in previous studies had a much lower detection rate. Malone *et al.* (1986) detected only 38% of tumours below 5 mm in diameter. Our results confirm their finding that tumour position was not important in ultrasound identification.

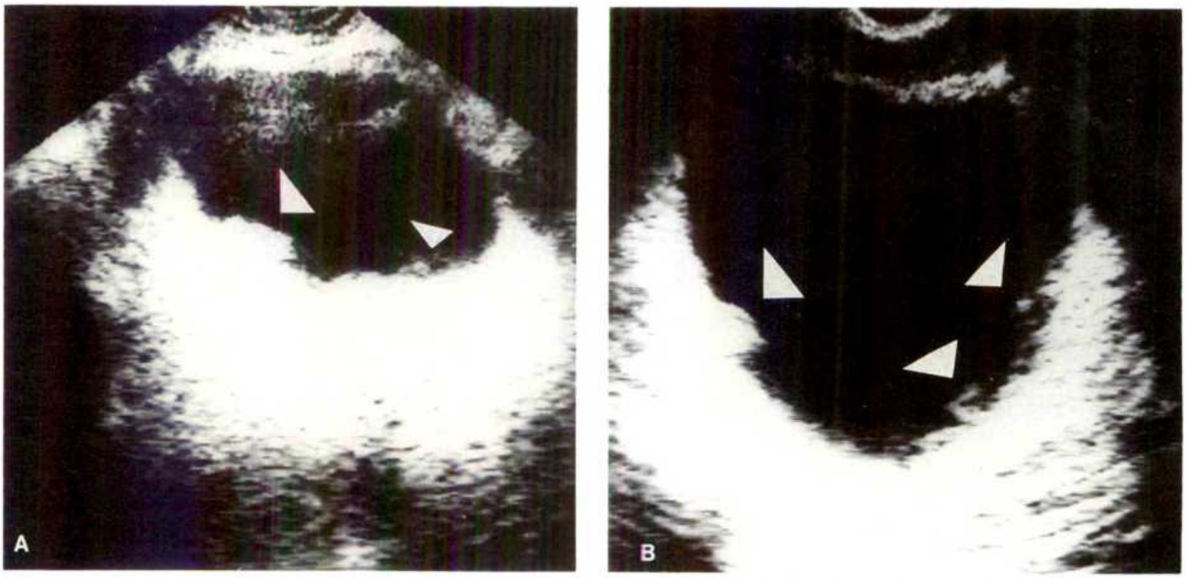

Fig. (A) Transabdominal scan showing 2 recurrent tumours. (B) Transrectal scan showing 3 recurrent tumours.

Table 4 Comparison of Series on Detection of Tumours by Transabdominal Ultrasound

	No of patients	*% Detected*
Itzchak *et al* (1981)	37	62
Brun *et al* (1984)	95	68
Malone *et al.* (1986)	126	50
Vallancian *et al.* (1986)	100	74
Juul *et al* (1986)	186	77

Combination ultrasound and cytology achieved a sensitivity rate of 100% and it is thus hoped to modify the practice of check cystoscopy by identifying those patients who have a recurrence and then subjecting them to operative treatment. It would probably be less invasive than flexible cystoscopy (Powell *et al.*, 1984).

The above results were obtained while the patient was under anaesthesia with a distended bladder. This is an optimal condition for ultrasound examination and studies are in progress to examine patients by ultrasound 1 week before cystoscopy, when the patient is requested to attend with a full bladder. By using this technique it may be possible to avoid unnecessary anaesthesia in elderly patients. It would also lead to financial savings, a decrease in operating time given over to check cystoscopies and a more convenient mode of follow-up from the patients' point of view. In addition, it is an easily learned technique which can be used by the urologist or radiologist.

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Absorption of Drugs from Continent Caecal Reservoir for Urine

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Summary—The possibility of drug absorption from a continent caecal reservoir for urine was studied in 3 men with well functioning reservoirs. Saline solutions of digoxin, theophylline or terbutaline were instilled into the reservoir, each on a separate occasion, and drug concentrations in plasma and urine were measured for 24 h thereafter. Theophylline, but not terbutaline or digoxin, was absorbed from the reservoir. Estimated from an intravenous reference dose, the uptake of theophylline from the reservoir was approximately 50%. In patients with this type of urinary diversion, therefore, reabsorption from the continent caecal reservoir may complicate drug therapy.

The most common indication for cystectomy and diversion of urine is carcinoma of the urinary bladder. The rising incidence of bladder cancer implies an increasing need for these procedures, if treatment continues along current lines. Interest in continent control of the diverted urine has grown steadily in the past decade. Such control can be achieved by means of a reservoir with an abdominal stoma. Bladder replacement is another example of continent urinary reconstruction. Bowel segments from various sites and of varying configurations have been used for both purposes.

Although numerous reports have dealt with the metabolic consequences of diverting urine via a bowel segment, the possibility of drug absorption from such a segment has attracted little or no interest. In patients with continent reservoirs or substitute bladders, where urine is in contact with the intestinal mucosa for periods of several hours, compounds such as drugs excreted in the urine may be reabsorbed. This could have implications for the recommended dosage.

The purpose of the present study was to explore the possibility of such drug absorption. The study was approved by the Ethics Committee of Lund/Malmö University Hospital and the patients gave written consent to participation.

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Patients and Methods

The study was performed on 3 men aged 46 to 67 years, all smokers, with well functioning continent caecal reservoirs for urine (Table 1). They had undergone cystoprostatectomy for bladder carcinoma 3 to 10 years earlier and all had received preoperative irradiation. Urinary diversion was accomplished via a continent caecal reservoir. To construct the reservoir an ileocaecal segment was isolated and the ureters implanted with antireflux technique into the caecum. An intussuscepted ileal nipple valve situated in the distal part of the ileum provided continence (Månsson *et al.*, 1984; Månsson and Colleen, 1987). The men usually emptied the reservoir at intervals of 4 to 5 h.

There were no signs of tumour recurrence or other abnormality, as judged from regular examination and screening before the study. The men took no regular medication.

Table 1 Participants

Patient no	*Age (years)*	*Weight (kg)*	*Height (cm)*	*Time after operation (years)*	*Pre-operative irradiation (Gy)*
1	46	85	185	8	45
2	51	81	178	3	20
3	67	71	176	10	45

On 3 occasions, separated by at least 1 week, a solution of digoxin (an aprotic drug) or theophylline (a weak acid, pka 9.2) or terbutaline sulphate (always ionised) was instilled into the emptied reservoir via a plastic or silicone catheter with the aid of a syringe. Previous *in vitro* experiments had shown no adsorption of any of the drugs to the plastic or silicone material. In these tests both catheter types were flushed with the respective drug solution and kept in the solution for 20 min. The drug concentration in the solution was determined before and after each *in vitro* test.

Drug solutions for the main study were prepared immediately before the start of each *in vivo* experiment. The following amounts were instilled into the reservoir: digoxin: 100 ml of a saline solution containing 0.38 mg digoxin (diluted Lanacrist solution for injection, Astra, Sweden), with estimated pH 6.8–7.2; theophylline: 150 ml of a solution for infusion containing 300 mg pure, anhydrous theophylline (Theo-Dur, Astra) with pH 4.0; terbutaline sulphate: 100 ml of a saline solution containing 5 mg terbutaline sulphate (diluted Bricanyl solution for injection, Astra), estimated pH 4.5.

The solutions administered had low buffer capacity. The exact dose given to each subject was determined by measuring the concentration of each solution and weighing the syringe and catheter before and after each instillation. The men were allowed to eat and drink freely, but caffeine beverages were not allowed during the theophylline experiment, to avoid metabolic interference. Blood samples (5 or 10 ml) were collected for assay of drug concentration in plasma in Na-heparinised Vacutainer tubes before (blank value) and 0.5, 1, 2, 4, 6, 8 and 24 h after drug administration. Urine was collected in tared polyethylene bottles (Noax, Sweden) before the study and in 3 fractions, 0–4, 4–8 and 8–24 h, after drug administration.

The blood samples were taken from an antecubital vein via a Venflon catheter or directly by venepuncture. Patency of the catheter was maintained by flushing with 2 to 3 ml heparinised (10 IU/ml) saline. To avoid contamination from the preceding sample or dilution by the saline flush, the first 2 ml of each blood sample was discarded. The samples were immediately centrifuged (1 400 g) for 10 min at room temperature. The plasma was collected and frozen at −20°C until analysis.

To obtain urine samples the reservoir was emptied as completely as possible via a plastic or silicone catheter. The men were requested to try to keep the urine in the reservoir throughout the first collection interval. Collected urine was weighed and, after careful mixing of the bottle's contents, samples were taken for freezing. Deviations from the prescribed procedure were noted.

In order to quantify absorption of theophylline, 200 mg of the drug (100 ml solution for injection) was given intravenously, after evaluation of results obtained with instillation into the reservoir, to patients 1 and 2. (Because of illness patient 3 did not receive intravenous theophylline). The drug was given as a 20-min infusion into an antecubital vein of the arm not used for sampling. Just before the start of the intravenous infusion the reservoir was emptied and 150 ml saline solution instilled into it. Blood and urine were sampled as already described, and an additional blood sample was taken at the end of the infusion.

Analytical procedures

Digoxin in plasma and urine was determined with radioimmunoassay (Smith *et al.*, 1969), by use of a commercial kit with digoxin ^{125}I as the tracer (Farmos Diagnostica, Åbo, Finland). In our hands the limit of quantitation (LOQ) was 0.3 nmol/l and the within-assay coefficient of variation (CV %) 5.3 at 1.3 nmol/l.

Theophylline in plasma and urine was assayed with liquid chromatography (Edholm *et al.*, 1986a, b). The method in plasma was capable of measuring down to 0.15 mg/l (LOQ) with CV % 0.5 to 2.7% at 1.4 mg/l. The method in urine was validated for another plasma xanthine (enprofylline) giving similar precision. That validation presumably applies also to theophylline, which elutes before enprofylline from the column but has similar detector response.

For assay of terbutaline in plasma and urine, gas chromatography plus mass spectrometery (Borgström *et al.*, 1988) was used. In plasma LOQ was 2 pmol, normally implying 1 nmol/l. CV % was 4.7% at this level. In urine the corresponding figures were 10 pmol (20 nmol/l at best) and 13.0%.

Pharmacokinetic evaluation

The following pharmocokinetic parameters were calculated when feasible: the area under the curve of plasma concentration vs time (AUC), the elimination rate constant (k), half-life ($t_{1/2}$), bioavailability (F) and recovery of drug in urine.

AUC was calculated with use of the trapezoidal rule and extrapolated to infinity by dividing the last measurable plasma concentration value by k. The rate constant was estimated from the terminal phase of the plasma concentration curve by log-linear regression. Half-life was calculated as ln 2/k. Bioavailability was the amount of the dose absorbed through the reservoir mucosa, and was calculated as discussed in connection with results. Urinary recovery was calculated as the amount of drug found in the urine divided by the administered dose.

Results

No measurable terbutaline concentrations were found in plasma, while the amount recovered from the urine was calculated as 102, 82 and 94%, respectively, of the given dose. Hence it seemed that terbutaline was not absorbed from the reservoir. In addition, the figures indicated almost complete recovery of urine.

Also in the digoxin experiments no measurable plasma concentrations were found. The urinary recovery of digoxin was only 70% (range 67–72%) of the dose. However, a test of the analytical method when applied to urine samples showed that it could recover only 76% of a spiked amount of digoxin. Our findings therefore indicated that digoxin was not absorbed from the reservoir.

The plasma concentrations of theophylline were measurable for 8 h after both caecal and intravenous administration (Fig.). The elimination rate constant, k, differed between the 2 administrations (half-lives given in Table 2). AUC extrapolated to infinite time is dependent on bioavailability (F), dose, volume of distribution (V) and k:

$$\mathrm{AUC_{cr}} = \frac{\mathrm{F \cdot Dose_{cr}}}{\mathrm{V \cdot k_{cr}}} \tag{1}$$

$$\mathrm{AUC_{iv}} = \frac{\mathrm{Dose_{iv}}}{\mathrm{V \cdot k_{iv}}} \tag{2}$$

The subscripts cr and iv denote, respectively, instillation into caecal reservoir and intravenous infusion.

V can be considered as a constant (Riegelman *et al.*, 1980). Division of equation 1 by equation 2 then gives

$$\mathrm{F} = \frac{\mathrm{AUC_{cr}}}{\mathrm{AUC_{iv}}} \cdot \frac{\mathrm{Dose_{iv}}}{\mathrm{Dose_{cr}}} \cdot \frac{\mathrm{k_{cr}}}{\mathrm{k_{iv}}} \tag{3}$$

Mean F was calculated as 50% (Table 2). The inter-individual differences in bioavailability were very small, although the time during which urine was retained in the reservoir during the first interval varied, *viz.* 3, 4 and 2.5 h. As only 1 man kept the urine in the reservoir for the scheduled 4 h, the observations indicated that most of the absorption took place within the first 2 to 3 h after drug administration.

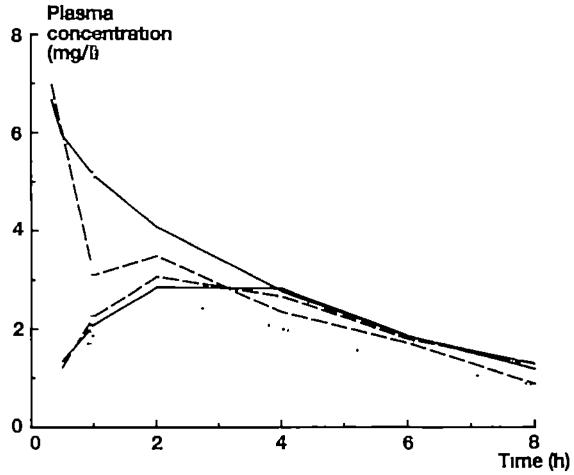

Fig. Plasma concentrations of theophylline during 8 h after instillation of 300 mg of the drug into the continent caecal reservoir in 3 cases (lower 3 curves) and after intravenous infusion of 200 mg in 2 of the same cases (upper 2 curves) ——— Patient No. 1. — — — Patient No 2. · · · · Patient No. 3.

The amount of theophylline recovered from the urine was 51.3% in the first fraction and 53% during 24 h (mean % of given dose). This comprised mainly unabsorbed drug, but also drug that had been absorbed and then excreted in the urine. It is known that about 10 to 20% of an absorbed theophylline dose is excreted unchanged in the urine (Dan-shya Tang-Liu *et al.*, 1982). The sum of the amount of theophylline found in the urine and the bioavailability should therefore have exceeded 100%, which indeed it did (mean 103%, Table 2).

Table 2 Pharmocokinetic Data on Theophylline Instilled into the Continent Caecal Reservoir for Urine

		% of dose		
Patient no.	*Half-life* (h)*	*Bioavailability*	*Urinary recovery*	*Bioavailability + urinary recovery*
1	3.8 (2.8)	49	55	104
2	3.2 (3.6)	54	45	99
3	3.3	47†	59	106
Mean		50	53	103

* Values within parentheses were found with the intravenous reference.

† A mean value from the i v curves of patients 1 and 2 was used to estimate the bioavailability in patient 3

Discussion

Studies with sustained-release terbutaline tablets (Nyberg and Kennedy, 1984) and calculations of absorption rate at different times after oral administration (P. O. Fagerström, personal communication) suggested that terbutaline is poorly absorbed through the colonic mucosa. Observations in the present study corroborated this evidence and were also in line with the demonstrated failure of instilled terbutaline to influence the motor activity of the caecal reservoir (Månsson *et al.*, 1989). Like terbutaline, digoxin was not absorbed from the reservoir. This contradicts earlier reports that orally and intrasigmoidally administered digoxin was absorbed from the sigmoid colon (Andersson *et al.*, 1975) and that sustained digoxin plasma levels were measured after rectal administration of the drug (Steiness *et al.*, 1974). Digoxin was shown to be absorbed via a carrier mechanism (Lauterbach, 1981) and possibly this process was extinguished in the reservoir. A general reduction of enzyme activity has been observed in ileal mucosa in contact with urine (Philipson *et al.*, 1983).

In contrast, theophylline—a weak acid—can be reabsorbed in a urinary reservoir constructed from the caecum. Reabsorption of methotrexate—also with weakly acid functional groups—from an ileal conduit has been described in a case report (Bowyer and Davies, 1987) and, despite the small area of gut mucosa, sufficed to cause toxicity. Glucose reabsorption from ileal conduit was found to mask glucosuria in some diabetic patients (Onwubalili, 1982; Sridhar *et al.*, 1983). Effective transmucosal absorption thus is possible. Since this absorption can be of high degree even during the brief contact in an ileal conduit, the potential problems presumably can be more significant in a continent reservoir or bladder substitute with a large mucosal area and storage of urine for some considerable time.

Exposure of the intestinal mucosa to urine alters the ultrastructure of the enterocytes, especially in the area of the adluminal cell surface. In the continent caecal reservoir for urine the mean height of the microvilli was found to be reduced from 0.9 μm (in controls) to 0.5 μm. Random orientation and numerical reduction of the microvilli were also seen (unpublished observations). As all adsorbed matter must traverse the adluminal part of the mucosa, it has been suggested that the absorptive capacity of intestinal mucosa in contact with urine will be reduced after urinary diversion (Hansson *et al.*, 1978). It also seems plausible, however, that the interstitial increase in inflammatory cells, mainly lymphocytes and eosinophils, that is present in a caecal urinary reservoir (Månsson and Willén, 1988) could reflect secondary damage resulting from increased permeability of the mucosa. If and to what extent ultrastructural changes in time alter the absorptive capacity of an intestinal segment after incorporation into the urinary tract is as yet unknown. Ileum and colon may differ in this respect. In the present study the results obtained with each of the 3 drugs were uniform in all patients and unrelated to time since surgery. Previous authors, however, found that absorption of the amino acid L-phenylalanine from an ileal urinary reservoir progressively decreased (Philipson *et al.*, 1983).

Both theophylline and methotrexate can be absorbed through intestinal mucosa in contact with urine. Whether or not the presence of acidic functions in the compounds is a prerequisite for such uptake cannot be concluded from this limited experience. Investigations with basic drugs are also required, and the influence of lipophilicity should be studied. Physicians must be aware of possible problems of dosage when treating patients with conduit or reservoir urinary diversion.

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Prostatectomy in the Over 80-year-old

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Summary—With an ageing population the demand for prostatectomy in the over 80-year-olds is increasing. This study assesses the place of prostatectomy in this age group.

All patients over the age of 80 who underwent prostatectomy in a 2-year period were studied retrospectively; 90 such patients underwent 94 operations, 90 of which were TURPs. Serious concomitant disease was found in 64 patients (71%) and 11 (12%) had had a previous prostatectomy at least 1 year before. The mean weight of tissue removed was 24.8 g. In 18 men histology showed malignant change.

Two men died from cardiovascular disease immediately after surgery (2.1%); a further 5 patients (7.8%) died within 6 months. Post-operative morbidity was high, with 64 patients (71%) developing complications. These were related to pre-operative urinary tract infections and uraemia. Nevertheless, at 6 weeks 72 patients (80%) were considered to have had a satisfactory result.

Prostatectomy in the over 80-year-old has a good long-term outcome. Although the morbidity rate is high, these patients should be considered for operation provided they undergo careful pre-operative assessment.

The mortality rate for prostatectomy in patients aged over 80 years is reported as 5%, increasing to 7.4% for those with severe cardiorespiratory disease (Singh *et al.*, 1973). Over the last decade the demand for surgery in this age group has increased. The combination of safer anaesthesia, especially the widespread use of spinal techniques, careful pre-operative investigation and the experience of the specialised urological units, should contribute to prostatectomy in the elderly becoming a safe operation. To confirm this we present a 2-year review of 94 consecutive prostatectomies performed in the over 80s.

Patients and Methods

Patients over 80 years old undergoing prostatectomy at Bristol Royal Infirmary between July 1985 and June 1987 were identified from the operating theatre records. For each patient, information regarding pre-operative medical condition, operative and anaesthetic details and subsequent follow-up was obtained from the case records.

Each patient was given a pre-operative cardiorespiratory score according to the criteria described by Singh *et al.* (1973) (Table 1). Comparisons were made between the pre-operative grades and subsequent morbidity or mortality. Pre-operative urinary infection, pre-operative uraemia, prostatic weight and histology were assessed in the same way.

Table 1 Grading of Cardiorespiratory Status

Grade 1
- No significant concurrent disease

Grade 2.
- Myocardial infarction or cerebrovascular accident more than 6 months before operation
- Congestive cardiac failure controlled on treatment
- "Benign" arhythmias.
- Hypertension requiring treatment
- Moderate chronic obstructive airways disease
- Diabetic requiring treatment

Grade 3.
- Myocardial infarction or cerebrovascular accident within 6 months before operation
- Uncontrolled ventricular ectopics.
- Complete heart block.
- Inadequate controlled congestive cardiac failure or severe chronic obstructive airways disease with gross limitation of normal daily activities

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Patients who were able to void spontaneously with no incontinence at the 6-week follow-up were considered to have undergone successful prostatectomy. Statistical analysis was performed using the chi-squared test.

Results

A total of 90 patients (mean age 82.2 years, range 80–90) was identified; 94 prostatectomies were performed, of which 90 were transurethral; 55 patients (61%) were admitted as emergencies and 28 (31%) were considered to have chronic retention. The mean residual urine for those in acute retention (n = 37) was 620 ml (range 200–900) compared with 1674 ml for those with acute on chronic retention (n = 12). Patients who had chronic retention without symptoms were not routinely catheterised.

Severe concomitant cardiorespiratory disease coexisted in 64 patients (71%); 40 (44%) belonged to grade 1, 35 (39%) to grade 2 and 15 (17%) to grade 3. Eleven patients (12%) had undergone previous prostatectomy (mean = 9.5 years, range = 1–30).

A pre-operative urine infection was present in 23 patients (26%). Spinal anaesthesia was used in 70 patients (78%). The mean weight of prostate removed was 24.8 g (range 2–150 g); 18 men had malignant prostates and in 5 patients there was demonstrable metastatic disease.

The peri-operative mortality rate was 2.1%. Both patients belonged to grade 1 on pre-operative cardiorespiratory assessment, but died of acute myocardial infarction on the evening of operation. Another 5 patients died from unrelated pathology within 6 months of operation.

The post-operative morbidity rate was high, with 64 patients (71%) developing significant complications (Table 2), 24 patients required re-catheterisation after resection, only 12 of these eventually undergoing successful trial without catheter. Four patients underwent a repeat operation, of which only 2 were successful. A total of 10 patients (11%) ultimately required long-term catheterisation.

Table 2 Immediate Post-operative Complications in 64 Patients

Urological	*No*	*General*	*No*
Incontinence	20	PUO	5
UTI	18	Confusion	7
Clot retention	17	Chest infection	2
Retention	15	Cardiac	3
Total	70		17

Factors shown to increase the urological complication rate included a pre-operative urinary tract infection prostatic resection of over 25 g and pre-operative uraemia. However, these factors did not increase the length of hospital stay, alter the eventual outcome or increase the peri-operative or 6-month mortality rate (Tables 3–5).

The pre-operative cardio-vascular grading system did not predict peri-operative morbidity or mortality, but of the 7 patients dying within 6 months of surgery only 2 were grade 1 (Table 6).

At 6 weeks, 72 patients (80%) were judged to have undergone a successful prostatectomy. Of the remaining 18 patients, 7 developed post-operative retention, failing at least 1 trial without catheter and requiring long-term catheterisation; 4 men were incontinent, of whom 3 eventually required permanent catheterisation; 3 patients were lost to follow-up and 4 had died. Permanent catheterisation was undertaken only in those patients considered unfit for further surgery or in whom an

Table 3 Effect of Pre-operative Infected Urine on Outcome

	Yes	*(%)*	*No*	*(%)*
Total no	23		71	
GU complications	17	74	30	42 ($P<0.01$)
Other complications	5	22	8	11 ($P=$ NS)
Mean post-op stay (days)	8·8		7.3	
Successful outcome	18	78	54	76
Died <6 weeks	2	8.7	3	4.2
Died 6 weeks–3 months	0		1	1.5

Table 4 Effect of Pre-operative Uraemia on Outcome

	Yes	*(%)*	*No*	*(%)*
Total no.	41		53	
GU complications	28	68	19	36 ($P<0.01$)
Other complications	8	19	5	9 ($P=$ NS)
Mean post-op. stay (days)	8.0		7.5	
Successful outcome	34	83	38	72
Died < 6 weeks	0		3	5.7
Died 6 weeks–3 months	2	4.9	1	1.9

Table 5 Effect on Outcome of Prostatectomy >25 g

	Yes	*(%)*	*No*	*(%)*
Total no.	25		69	
GU complications	17	68	30	43 ($P<0.05$)
Other complications	2	8	5	11 ($P=$ NS)
Mean post-op stay (days)	7.7		7.6	
Successful outcome	18	72	54	78
Died <6 weeks	0		3	4.3
Died 6 weeks–3 months	0		3	4.0

Table 6 Mortality Related to Cardiorespiratory Status

	Grade I (%)	*Grade II (%)*	*Grade III (%)*
No of patients	40	35	15
1 month	2 (5)	0 (0)	0 (0)
3 months	2 (5)	1 (2.8)	1 (6.8)
6 months	2 (5)	3 (8.6)	2 (13)

adequate prostatectomy was considered to have been performed.

Discussion

Early reports on prostatectomy in the over 80s considered the surgical risk to be great and the mortality too high. In 1936 Twinem reported 40 such patients who had been submitted to open operation with a mortality rate of 33%. These figures contrast with those of Young and Davis (1926), whose operative mortality rate for all patients was 16%. It is little wonder, therefore, that at that time few elderly patients were submitted to prostatectomy. In fact, only 1 man over 80 years of age had a prostatectomy in the Massachusetts General Hospital during 1926–1930 (Swan and Mintz, 1931).

With the advent of transurethral surgery it was assumed that mortality would be lower. However, Lytton *et al.* (1968) still reported a peri-operative mortality rate in excess of 10% in elderly patients. Sach and Marshall (1977) had a 5% mortality rate, but only 24% of their procedures were endoscopic. In the present study, in which 96% of the prostatectomies were endoscopic, the mortality rate was reduced to 2.1% reflecting better operative management.

The peri-operative grading system of cardiorespiratory disease proposed by Singh *et al.* (1973) showed no correlation with peri-operative mortality, both of the deaths occurring in grade 1 patients. Although at 6 months 13% of patients in grade 3 had died as opposed to 5% in grade 1, there was no difference in the number of patients within each grade when compared with the reports of Singh *et al.* (1973) and Sach and Marshall (1977).

This study failed to confirm the findings of Sach and Marshall (1977) that pre-operative urinary tract infection influenced mortality. Renal impairment, also thought to have an adverse effect on mortality rates (Singh *et al.*, 1973), was not a contributory factor in this study.

Peri-operative morbidity, although not affecting the eventual outcome, remained surprisingly high, with 71% of patients developing either a urological or general complication. Pre-operative urinary tract infection, uraemia and prostatic resection >25 g all signficantly increased the urological but not the general complication rates. This correlation was surprising, since any patient with a proven urinary tract infection received peri-operative antibiotics. Such prophylactic treatment should be started well in advance of surgery.

No urological factors were identified as capable of predicting the general complication rate. With respect to the cardiorespiratory grading system, there was no correlation with complications, 54% being grade 1, 38% grade 2 and only 8% grade 3.

Although post-operative morbidity was high, the complications were mostly urological, short lived and had no effect on the eventual operative outcome. A success rate of 80% in this elderly population must be considered acceptable, comparing favourably with the long-term results in a recent study of patients of all ages (Malone *et al.*, 1988). Patient selection, however, still remains of considerable importance. We suggest that patients with faecal incontinence, significant mental confusion or both in combination should not be considered for prostatectomy. Apart from this small group, modern-day anaesthetic care and transurethral surgery mean that very few patients need suffer the problems of permanent catheter drainage.

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Enhanced Cavernometry: Procedure for the Diagnosis of Venogenic Impotence

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Summary—A technique of cavernometry to diagnose corporovenous leakage (CVL) is described. The criterion used to define CVL was a corporeal infusion rate >60 ml/min after the intracorporeal injection of 60 mg papaverine or 30 mg papaverine and 1 mg phentolamine. Alpha blockade in addition to papaverine decreased the incidence of corporovenous leakage.

Corporovenous leakage has become a recognised cause of impotence. Although the incidence of CVL has not been accurately determined, it may account for at least 25% of the causes of erectile dysfunction (Lewis, 1988). The venous closure mechanism has recently been described in anatomical dissections and physiological studies by Lue *et al.* (1986). Although Lowsley and Bray (1936) were the first to perform surgery for CVL, it has only been within the last 5 years that criteria for establishing this diagnosis using cavernometric studies have been established. Virag *et al.* (1984a and b) were the first to employ vasoactive agents during corporeal infusion studies. Wespes and Schulman (1985) defined CVL according to specific infusion rates to dilute saline. Lewis and Pryan (1986) categorised 3 groups of patients according to flow requirements during cavernosal infusions: those with full erections, those with incomplete rigidity and those who were unable to achieve any erectile capacity. In 1986, the Society for the Study of Impotence, a group of investigators collaborating together in the United States, presented its early findings concerning CVL at the annual meeting of the American Urological Association in New York. In that study, CVL existed if full rigidity could not be maintained with a saline infusion of less 60 ml/min after 60 mg intracavernosal papaverine. Recently, Padma-Nathan and Goldstein (1987) defined CVL according to the change in corporeal blood flow during the cavernometric study. In this study, a simplified technique to establish the diagnosis of CVL is described following the intravernosal injection of vasoactive drugs.

Patients and Methods

Over a 3-year period, 134 patients were selected from a total of 540 patients initially evaluated with a complaint of sexual dysfunction. The age range was 17 to 76 years (average 51.9); 65 patients had no concurrent medical problems, 24 had a history of hypertension, 18 diabetes mellitus, 9 coronary artery disease, 3 peripheral vascular disease, 2 lymphoma, 2 bladder cancer, 2 alcoholism, 2 hypothyroidism, 2 obesity, 2 Peyronie's disease, 1 hyperthyroidism, 1 hyperlipidaemia and 1 had had a pelvic fracture.

Patients were selected according to the following criteria:

1. History of decreased rigidity or loss of erection without ejaculation.
2. Poor response to vasoactive drugs.
3. Primary impotence and normal endocrine studies.
4. Candidates for revascularisation.

There were two groups of patients. The first consisted of 27 patients who were injected with 60 mg papaverine intracorporeally prior to cavernometry. The second group included 115 patients. They were injected with a combination of 30 mg

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Table Cavernosometry

	Category			No of patients
	I (<60 ml/min) (%)	*II* (>60 ml/min) (%)	*III* (*No erection*) (%)	
60 mg papavarine	5 (19)	5 (19)	17 (62)	27
30 mg papavarine + 1 mg phentolamine	64 (55)	29 (25)	22 (20)	115

papaverine and 1 mg phentolamine prior to cavernometry. After the cavernosal injection of either 60 mg papaverine or 30 mg papaverine and 1 mg phentolamine, the patient was observed for up to 30 min. Cavernometry was performed if he did not have a full normal response to the vasoactive drugs. His penis was prepared with either alcohol or Betadine and a #21 scalp vein needle inserted into one of the corpora cavernosa near the base of the penis. An anaesthesia I.V. tubing may be placed on the scalp vein needle but it is not necessary. Approximately 500 ml of injectable normal saline were made available. Two 60 ml Luer-Lok syringes were used for the infusion. Any timing mechanism can be used to assess the volume/ min fluid requirement to maintain or produce the normal full erectile state. The amounts of fluid used to produce and to sustain the erection/min were recorded. When the study was completed, the scalp needle was removed and direct pressure applied to the puncture site for 2 to 3 min.

Results

Three classifications were noted in the cavernometric group (Table):

(I) Normal: normal rigidity with a flow requirement of <60 ml saline/min.
(II) Moderate CVL: normal rigidity with a flow requirement >60 ml saline/min.
(III) Severe CVL: inability to produce normal rigidity regardless of volume of fluid used.

In group I, 27 patients were injected with 60 mg papaverine alone prior to cavernometric studies. Only 5 (19%) were normal (category I); 5 (19%) were in category II and 17 (62%) in category III. When the combination of 30 mg papaverine and 1 mg phentolamine was used, a marked change was noted in the distribution of patients in the 3 categories: I—64 patients (55%), II—29 patients (25%) and III—22 patients (20%). No cardiovascular complications were noted and no patient required follow-up care for local complications related to the needle puncture. Some patients were studied on a table with X-ray capability and underwent cavernography following the cavernometry study.

Discussion

In the early part of the study (the first 27 patients), when papaverine alone was used to maximise the arterial response, the incidence of CVL was 81%. This high incidence could have been real, related to a high index of suspicion of CVL because of the selection criteria used. However, after it was noted by Zorgniotti and Le Fluer (1985) and Brindley (1983) that the use of alpha-blocking agents enhanced the vascular response, the combination of 30 mg papaverine and 1 mg phentolamine was used to enhance the normal arterial response and venous closure mechanism. A better tumescent response was noted and the next 115 patients studied demonstrated a 55% normal response. No prolonged erection episodes were noted in follow-up, which was most likely due to the dilutional effect of the vasoactive agents by the volume of saline used. Cavernometry has been shown to be a safe, uncomplicated procedure.

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Effect of Histamine on Human Vas Deferens *in vitro*

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Summary—Histamine, 2-methylhistamine and 4-methylhistamine produced concentration-related contractions in some isolated human vas deferens preparations. The contractions produced by histamine and its analogues were reversibly and competitively antagonised by the H_1-receptor blocker, mepyramine, but not the H_2-receptor blockers, burimamide and cimetidine. Phentolamine, atropine and guanethidine did not affect the excitatory action of histamine. Histamine and 4-methylhistamine did not show any inhibitory effect on KCl-induced tone. The results showed that histamine receptors were present in the human vas deferens and the histamine receptors mediating the excitatory response were likely to be H_1-receptors.

Histamine was reported to be a constituent of human ejaculate, although its origin was not traced (Katsh, 1959). Relatively high levels of histamine were found in the male sexual accessory tissues such as the testes, seminal vesicles, prostate glands and the vas deferens of the rat, mouse and rabbit (Moulton, 1969). The action of histamine and the nature of its receptor in the vas deferens of these animal species are known. In the mouse vas deferens, histamine produced only relaxation via H_2-receptors, but in the vas deferens from rabbit and guinea-pig histamine produced contraction via H_1-receptors (Bhalla and Marshall, 1981; Vohra, 1981). These findings illustrate species differences in histamine receptors in the vas deferens. The presence of histamine H_1- and H_2-receptors in isolated human corpus cavernosum muscle has been reported (Adaikan and Karim, 1977).

The aim of the present study was to investigate the pharmacological action of histamine and to identify and characterise histaminergic receptors in the human vas deferens using specific H_1- and H_2-receptor agonists and antagonists.

Materials and Methods

Macroscopically normal specimens of human vas deferens from transsexual patients undergoing gender reassignment surgery were collected and transferred to the laboratory in cold Krebs-Henseleit solution immediately after the operation. Strips of vas deferens, 1½ to 2 cm long, free from adjacent tissue were mounted in 10-ml organ baths containing Krebs-Henseleit solution maintained at 37°C and aerated with 95% oxygen in carbon dioxide. The pH of the solution was 7.4. The Krebs-Henseleit solution was of the following composition (mM): sodium chloride 115, potassium chloride 4.7, calcium chloride 1.8, potassium dihydrogen orthophosphate 1.2, magnesium sulphate 1.2, glucose 8.5, sodium bicarbonate 22.1 and disodium EDTA 0.03.

An initial tension of 1.5 g was applied to the muscle strips, which were allowed to equilibrate for 1 h before the effects of drugs were tested. The response of the tissue to drugs was registered isometrically using a force transducer or isotonically with a frontal lever connected to a recorder. Regardless of whether isometric or isotonic recording was used, the responses of the tissue to drugs were qualitatively similar. A contact time of 2 to 4 min and a cycle time of 15 min were used for each agonist. Antagonists, when used, were applied 1 min prior to the addition of the agonist.

Concentration-response curves for noradrenaline, histamine and 2-methylhistamine were obtained in a non-cumulative manner by adding increasing doses of the agonists at 15-min intervals.

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The agonist was removed when the contractile response reached its peak. The potency of histamine and 2-methylhistamine relative to noradrenaline was estimated by 4 point bioassay.

The possibility of histamine and 4-methylhistamine having a relaxant effect was investigated in muscles whose resting tone was raised with potassium chloride.

The following compounds were used: histamine dihydrochloride (Merck), 2-methylhistamine dihydrochloride (Smith, Kline & French), 4-methylhistamine dihydrochloride (Smith, Kline & French), acetylcholine chloride (Sigma), noradrenaline bitartrate (Sigma), mepyramine maleate (May & Baker), burimamide (Smith, Kline & French), cimetidine (Smith, Kline & French), phentolamine mesylate (Ciba), atropine sulphate (Merck) and guanethidine sulphate (Ciba). All concentrations were expressed as the final concentrations of the free base in organ bath fluid.

Stock solutions of all drugs were kept frozen at −10°C and diluted to the required concentrations in physiological saline (0.9% w/v) before use on the day of the experiment.

Results

Effect of histamine and its analogues

The full concentration-related response of histamine was investigated in 25 strips. Histamine acted as a full agonist in 10 strips with mean maximal contractions comparable to those obtained with noradrenaline. Figure 1 shows a representative tracing of the contractile responses to histamine and noradrenaline in isolated human vas deferens. In the remaining 15 strips, lower concentrations of histamine contracted while increasing concentrations of histamine produced smaller contractile responses or none at all. The mean maximal response obtainable for histamine was only about 30% of the maximal responses due to action of noradrenaline at α-adrenoceptors in these strips.

2-methylhistamine (2-meH) and 4-methylhistamine (4-meH), which are respectively H_1- and H_2-histamine receptor agonists, produced concentration-related contractions in only some of the strips; 4-meH was much weaker than histamine and 2-meH, requiring a higher threshold concentration in eliciting an excitatory response. The mean threshold concentrations for histamine, 2-meH and 4-meH were 4.3, 23 and 1160 μM respectively (Table). Histamine and 2-meH were respectively 2.4 and 33 times less potent than noradrenaline in contracting these strips.

In 4 strips pre-contracted with potassium chloride (40 mM) to elevate the tone of the strips, histamine (0.9–180 μM) and 4-meH (5.8–580 μM) did not show any relaxant action but caused further contraction in 2 strips. Pre-treatment of the strips with mepyramine (0.14 μM), which abolished the excitatory action of histamine and 4-meH, also failed to produce a reversal of effect.

Effect of antagonists

Mepyramine, a selective H_1-receptor antagonist at concentration range 0.03 to 0.35 μM, inhibited dose-dependently the contractile response to histamine, 2-meH and 4-meH (n = 4 each) by 15 to 100% (Figs 2 and 3). The inhibitory effect was reversible upon removing the antagonist from the bathing fluid.

Burimamide (0.09–1.9 μM) and cimetidine (1–200 μM), which are selective H_2-receptor antagonists, potentiated the contractile action of histamine in 50% of the strips and had no effect on the remaining strips. Contractions produced by 2-meH

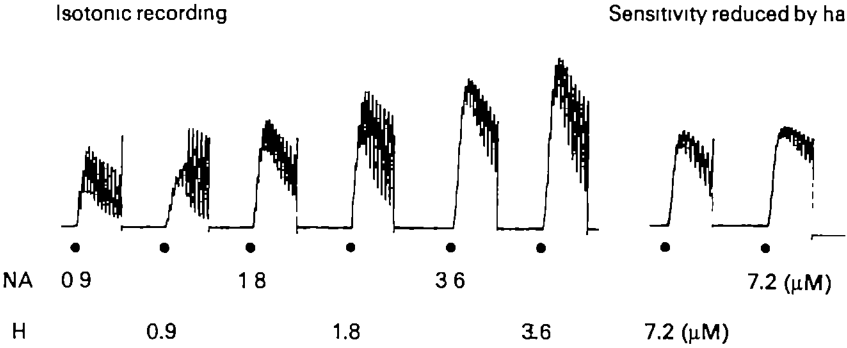

Fig. 1 A representative tracing showing concentration-response relationship of noradrenaline (NA) and histamine (H) in isolated human vas deferens

Table Threshold Concentrations and Potencies of Histamine, 2-methylhistamine (2meH) and 4-methylhistamine (4meH) on Isolated Human Vas Deferens

	No	*Threshold concentration (Mean ± SEM) (µM)*	*Potency (Mean ± SEM)*
Noradrenaline	10	0.9 ± 1.0	1
Histamine	10	4.3 ± 1.0	0.41 ± 0.10
2meH	3	23 ± 7	0.03 ± 0.01
4meH	12	1160 ± 240	–

and 4-meH in all of the strips tested were unaltered in the presence of burimamide or cimetidine (Figs 4 and 5). However, contractions produced by noradrenaline were inhibited (range 11–97% of control response) by mepyramine, burimamide and cimetidine in at least 50 to 75% of the strips tested.

Phentolamine (0.04–1.8 µM), atropine (1.7–3.4 µM) and the adrenergic neurone blocker, guanethidine (5–20 µM), all had no influence on the contractile response to histamine (n = 3—6 each).

Discussion

This study showed that histamine and its analogues produced contractions of the isolated human vas deferens. The contractile responses to histamine, 2-meH and 4-meH were blocked by the H_1-receptor antagonist, mepyramine, but not the H_2-receptor antagonists, burimamide and cimetidine. Other antagonists such as phentolamine and atropine,

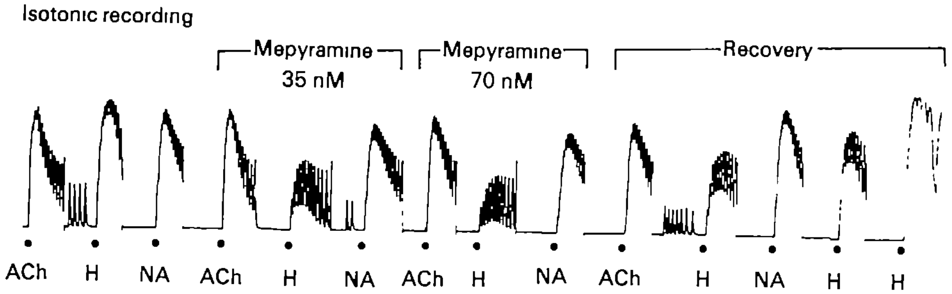

Fig. 2 Effect of mepyramine on responses to acetylcholine (ACh, 140 µM), histamine (H, 4.5 µM) and noradrenaline (NA, 3 µM) in isolated human vas deferens.

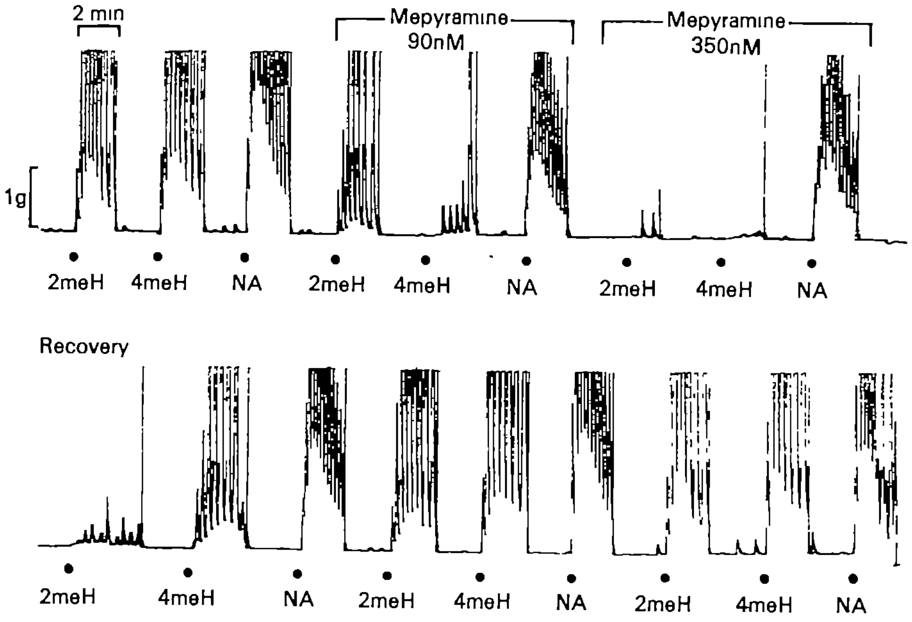

Fig. 3 Effect of mepyramine on responses to 2-methylhistamine (2meH, 135 µM), 4-methylhistamine (4meH, 880 µM) and noradrenaline (NA, 1.2 µM) in isolated human vas deferens

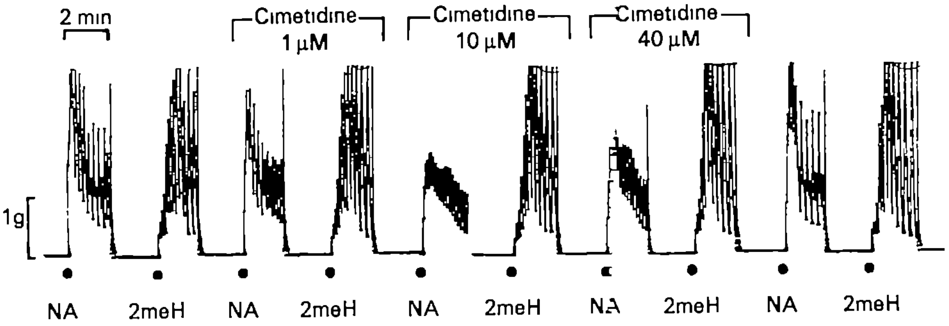

Fig. 4 Effect of cimetidine on contractile responses of isolated human vas deferens to noradrenaline (NA, 1 2 µM), histamine (H, 14 µM) and 4-methylhistamine (4meH, 2mM)

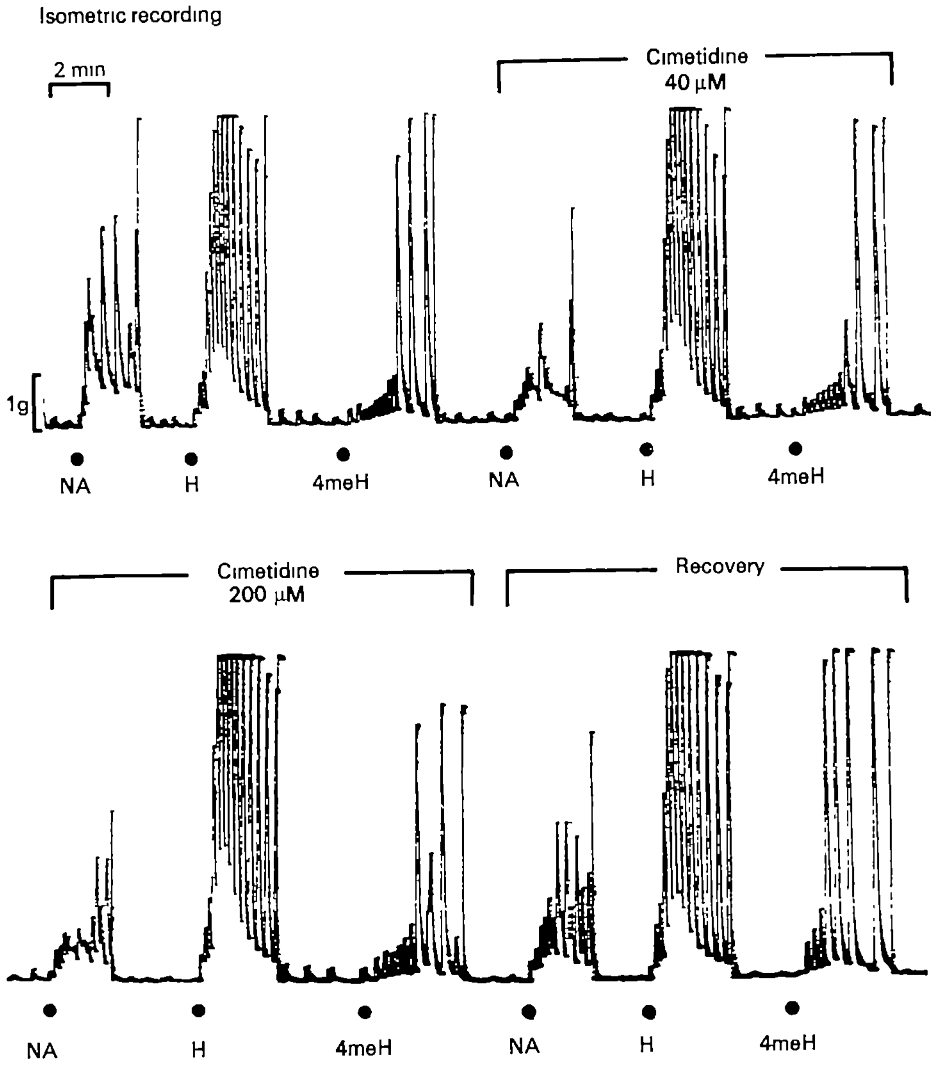

Fig. 5 Effect of cimetidine on contractions produced by noradrenaline (NA, 6 µM) and 2-methylhistamine (2meH, 350 µM) in isolated human vas deferens.

which specifically blocked the contractions produced by noradrenaline and acetylcholine respectively, did not influence the response to histamine. The lack of effect of guanethidine on the action of histamine showed that histamine was not acting indirectly via adrenergic nerves. Thus discrete histamine receptors were present in the human vas deferens and the histamine receptor mediating the excitatory response was likely to be H_1-receptor. Histamine H_1-receptor in the human vas has also been reported by Calvete *et al.* (1984).

The inability of H_2-receptor antagonists to inhibit the contractile action of the H_2-receptor agonist, 4-methylhistamine, indicated that excitatory H_2-receptors were not involved. Thus it is likely that the contractile response of the human vas deferens to 4-methylhistamine, which was inhibited by mepyramine, was the result of 4-methylhistamine activating H_1-receptors rather than H_2-receptors. Furthermore, it has been shown that 4-methylhistamine was only about 5 times as potent at H_2—as it was at H_1-receptors in the guinea pig ileum (Barker and Hough, 1983), though 4-methylhistamine is regarded as a fairly selective H_2-receptor agonist.

Inhibitory H_2-receptors were present in the rat and mouse vas deferens, as indicated by the observation that histamine depressed the twitch response to field stimulation and that this inhibitory effect was partially or fully reversed by cimetidine but not by mepyramine. In addition, the H_2-receptor agonists, dimaprit and 4-methylhistamine, mimicked the inhibitory action of histamine (Bhalla and Marshall, 1981; Vohra 1981). In the present study, the facilitatory effect of cimetidine and burimamide on histamine but not 2-methylhistamine and 4-methylhistamine, as observed in some human vas deferens preparations, suggested that inhibitory H_2-receptors might be present. However, this could not be confirmed, since histamine did not relax but caused further contraction in the presence of KCl. Moreover, mepyramine did not cause a reversal of the excitatory action of histamine.

The excitatory histamine receptors in the rabbit and guinea-pig vas deferens were predominantly H_1 (Joshi and Verma 1981; Vohra, 1981; Bhalla and Marshall, 1981). Excitatory H_2-receptor may also be present in the guinea-pig vas deferens, as suggested by the finding that contractile responses to 4-methylhistamine were blocked by metiamide (Joshi and Verma, 1981).

The observation that both H_2-receptor antagonists, burimamide and cimetidine, exerted an inhibitory effect on noradrenaline-induced contraction of human vas deferens implicated the involvement of H_2-receptors in the motor action of noradrenaline. In addition to competitive and specific blockade of histamine H_2-receptors, burimamide and cimetidine are known to possess blocking activities on both post-junctional α-adrenoceptor in rabbit aorta and pre-junctional α-adrenoceptor in the isolated guinea-pig atria (McCulloch *et al.*, 1979). Thus it is possible that a similar interaction between noradrenaline and H_2-receptor antagonists occurs in the human vas deferens.

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Case Reports

Penile Plaque: a Presentation of Metastatic Renal Carcinoma

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Case Report

A 49-year-old man presented with a hard intracorporeal plaque midway down the shaft of his penis, 7 years prior to this he had had a right nephrectomy for a stage 1 renal carcinoma There had been no evidence of recurrence after 5 years and he had been discharged from follow-up.

Biopsy of the lesion revealed metastatic adenocarcinoma identical to that in the kidney removed 7 years previously. Bone scan and CT scan of the thorax, abdomen and pelvis were normal.

A wide local excision of the area was performed, removing the tumour together with a substantial section of the right corpus cavernosum. A compensatory tuck in the contralateral side of Buck's fascia was made to preserve a normal appearance without expectation of maintaining erectile function. Histology showed that the resection margins were clear of tumour. Six months later there was no sign of local or distant spread. Both erectile and ejaculatory function had returned, although the erect penis deviated toward the side of the excision despite the compensatory tuck.

Comment

Penile metastases are very rare (Abeshouse and Abeshouse, 1961). They are usually multiple and are a manifestation of advanced malignancy (Karanjia *et al.*, 1987). Subsequent prognosis is therefore poor. The most common primary tumours are bladder and prostate, but metastases from renal carcinoma have been reported (Abeshouse and Abeshouse, 1961). It is also unusual for metastases from renal carcinoma to remain dormant for as long as 7 years after removal of the primary. Solitary metastases presenting late, as in the present case, are usually associated with a better prognosis than primary tumour and solitary metastasis presenting together (O'Dea *et al.*, 1978).

In view of the poor outlook, surgical treatment is indicated only if there is no evidence of further spread. Provided the resection margins are clear and the distal vasculature is preserved, partial or complete amputation can be avoided. Even after extensive resection of the corpus cavernosum both a relatively normal appearance and erectile function can be maintained.

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Seminal Vesicle Cystic Dilatation Masquerading as Proctalgia Fugax*

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Case Report

A case is reported of cystic seminal vesicle with ipsilateral renal agenesis in a 27-year-old male who presented with a 4-year history of increased frequency of urine, painful ejaculation and recurrent deep rectal pain previously diagnosed as proctalgia fugax. Rectally, a mass was felt anteriorly above the prostate. Urography revealed an absent right and hypertrophied left kidney. Transabdominal pelvic sonography and CT scan demonstrated a cystic lobulated mass (7.0 × 3.1 cm) behind the bladder (Fig.) Cystoscopy revealed trigonal asymmetry with an absent right ureteric orifice The operative approach was through a Czerny incision. The right ureter ended in a cystic seminal vesicle. The blind ureter and seminal vesicle were excised. Histopathology confirmed a benign multiloculated cyst. The patient was asymptomatic at follow-up 4 months later

Comment

Seminal vesicle cysts are rare. The common origin of the vas, seminal vesicle and ureter from the mesonephric duct explains the frequency of associated malformations of the ipsilateral renal unit. The lateral origin of the ureteric bud prevents its

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*Based on a Poster Demonstration at the Asian Pacific Congress of the International College of Surgeons in Taiwan, 1987

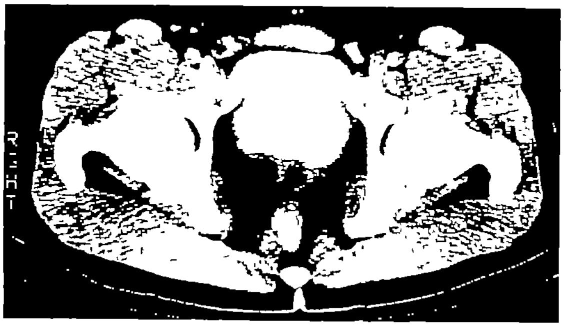

Fig. CT scan after intravenous contrast showing multicystic lesion behind the bladder

absorption into the bladder and results in its ending in the seminal vesicle. The ureteric bud does not contact the metanephrogenic cap on its upward ascent, thus resulting in an absent kidney (Tanagho, 1976).

Painful ejaculation and findings on rectal examination should alert the urologist. IVU, ultrasonography and computed tomography confirm the diagnosis. We do not recommend vasovesiculography or cyst puncture for diagnosis or treatment of the cyst, as they are prone to recurrence and infection (Hart, 1966). The treatment of such malformations should be restricted to symptomatic cases and consists of vesiculectomy (Roehborn *et al.*, 1986).

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AIDS presenting as Cytomegalovirus Cystitis

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Case Report

A 43-year-old Tanzanian black male, visiting the UK, presented with strangury, severe frequency and haematuria. He had a tender bladder, pyrexia and small, palpable inguinal lymph nodes; the other systems were normal. MSU showed pyuria and grew *Escherichia coli*. Antibiotics eradicated this infection but did not improve his symptoms.

Blood count showed 5.3 × 10^9 leucocytes/l (eosinophils 2%). No ova were detected in the urine, although schistosomal serology by ELISA was positive (positive predictive value 63%). An intravenous urogram showed irregular bladder mucosa near the left ureteric orifice; ureters and kidneys were normal. On cystoscopy the bladder was of small capacity with reddened oedematous mucosa, almost polypoid in areas.

Bladder biopsy showed an acute-on-chronic cystitis with lymphoid follicles, urothelial ulceration and regenerative hyperplasia. Urothelial cells and endothelial cells in the submucosa had enlarged nuclei with eosinophilic inclusions, consistent with cytomegalovirus (CMV) Immunocytochemical staining for CMV (monoclonal antibody from Dakopatts Ltd) was positive (Fig.). Electron microscopy of re-processed material from the biopsy showed 100 nm herpes virus particles, consistent with CMV, in urothelial cell nuclei There was no evidence of tuberculosis or schistosomiasis.

The patient's serum was total CMV antibody positive by latex agglutination (Becton Dickinson), although no

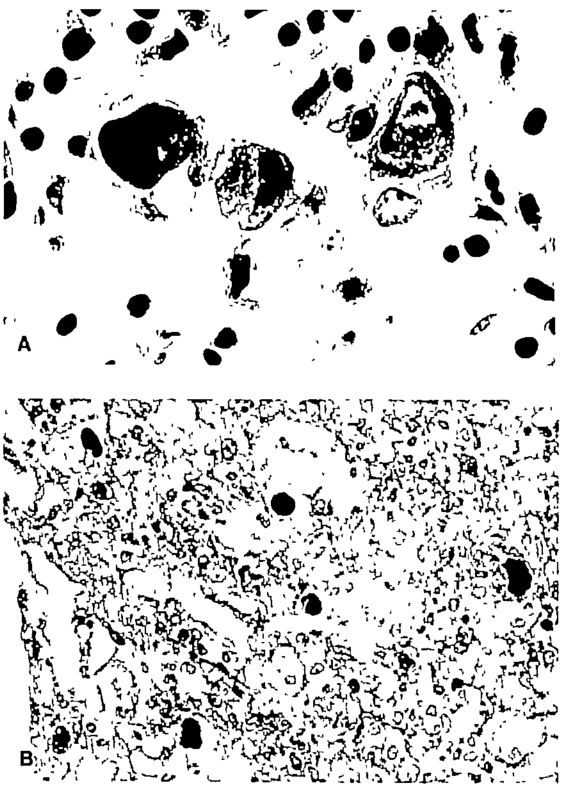

Fig. (A) Cells with enlarged nuclei and prominent nucleoli (H and E ×1000) (B) Immunoperoxidase anti-CMV stains several nuclei, confirming identity of CMV (×400)

CMV IgM was detected by ELISA (Mercia Diagnostics) Human immunodeficiency virus (HIV-1) antibody was present by competitive ELISA (Wellcome), antiglobulin ELISA (Abbott) and by gelatin particle agglutination assay (Fujirebo).

Comment

The diagnosis of cytomegalovirus cystitis in an HIV seropositive patient satisfies the criteria for the acquired immunodeficiency syndrome (AIDS) (Harawi, 1989). This patient had no other clinical features of AIDS at presentation and has since returned home.

In AIDS patients with multi-organ CMV infection, CMV cystitis is occasionally noted (Reichert *et al.*, 1983) and CMV epididymitis has been reported (Randazzo *et al.*, 1986). To our knowledge this is the first report of CMV infection in an HIV seropositive person manifesting clinically as cystitis only.

Urologists should be aware of this presentation of AIDS.

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Small Bowel Lymphoma Invading the Bladder

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Case Report

A 72-year-old woman presented with a 3-week history of a tender lump in the right lower abdomen. Direct questioning revealed a 4-week history of painless haematuria. Clinical examination confirmed a smooth, oval mass situated in the hypogastrium to the right of the midline. It was approximately 10 cm in diameter and particularly mobile in a transverse rather than a vertical direction. Pelvic examination suggested that the uterus was separate from the swelling. Ultrasound showed a solid mass closely related to and above the bladder and uterus. An intravenous urogram and a barium enema were both normal Cystoscopy revealed a pearl-white umbilicated lesion 1 cm in diameter invading the bladder vault Biopsies were reported as non-Hodgkin's lymphoma.

Laparotomy was performed and a large tumour with matted loops of adherent small intestine was found in the terminal ileum invading the bladder. Despite the extensive local nature of the lesion there was no evidence of metastatic spread and a radical hemi-colectomy with partial cystectomy was undertaken *en bloc*. Frozen and subsequent paraffin sections confirmed that the free margins of the bladder and the mesenteric lymph nodes were uninvolved with tumour. The patient made an uninterrupted recovery.

Comment

Malignant small intestinal tumours are rare and lymphomas comprise but 7%. Symptoms are often vague and insidious, with the commonest presentation being either an abdominal mass or small intestinal obstruction (O'Rourke *et al.*, 1988). There is a well known association with coeliac disease. Barium studies frequently fail to demonstrate the lesion and it is unusual to achieve a pre-operative diagnosis (O'Rourke *et al.*, 1988).

Vesico-enteric fistulation from carcinoma of the colon, Crohn's disease and tuberculosis of the small intestine have been documented but we have found no reports of lymphoma of the ileum invading the full thickness of the bladder wall and presenting with haematuria.

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Cystic Prostatic Carcinoma

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A case of latent carcinoma of the prostate presenting clinically as a prostatic cyst is reported.

Case Report

A 55-year-old man presented with symptoms of prostatism associated with tenesmus and rectal pain. Rectal examination revealed a soft mass within the left lobe of the prostate.

Transrectal ultrasound confirmed the presence of a cystic mass 5 cm in diameter within the left lobe of the prostate compressing the rectum (Fig.). The rest of the prostate was considered benign. The left lobe was partially resected following ultrasonically controlled transperineal needle drainage of 30 ml of brown fluid.

Cytological examination of the cyst fluid revealed no malignant cells but histological examination of the resected prostatic tissue revealed a well differentiated invasive prostatic carcinoma. The serum prostatic specific antigen level was 92 μg/l (normal range = 0–4 μg/l) and a bone scan was normal.

The patient subsequently completed a course of pelvic radiotherapy (4600cGy over 4½ weeks) but within 5 months his cyst had refilled, requiring further drainage.

Comment

Despite being the fifth most frequent cancer in men, with an estimated 197,000 cases occurring annually worldwide (Parkin *et al.*, 1984), prostatic carcinoma presenting as a cystic rather than a solid lesion has not previously been reported.

Small benign prostatic cysts, although frequently encountered at autopsy, rarely attain a diameter greater than 1 cm and are clinically insignificant. They are classified into 4 types: Müllerian duct, seminal vesicle, ejaculatory and retention cysts (Bucknall and Lord, 1981). A post-gonococcal and a benign dermoid cyst have also been reported in the prostate (Bucknall and Lord, 1981; Uthmann and Terhorst, 1981).

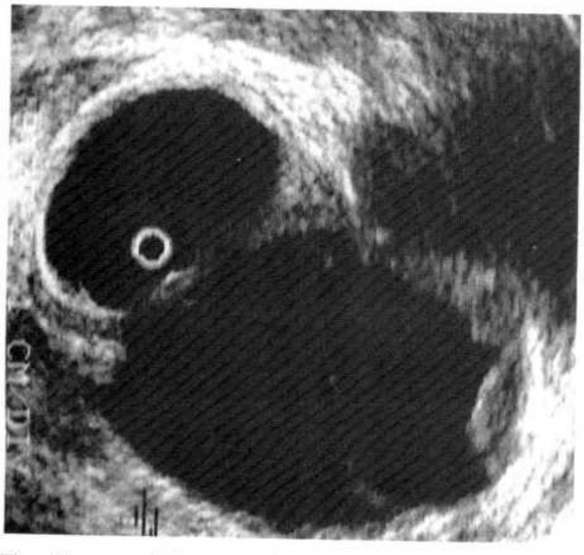

Fig. Transrectal ultrasound showing large prostatic cyst compressing the rectal wall. (Freq. = 4.0 MHz, FOCL = 3–7 cm).

Although in our patient the cyst may belong to one of the above categories, this is the first reported case of latent carcinoma of the prostate presenting with symptoms directly attributable to a cystic lesion.

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Leaking Iliac Artery Aneurysm causing Bilateral Ureteric Obstruction and Oliguria

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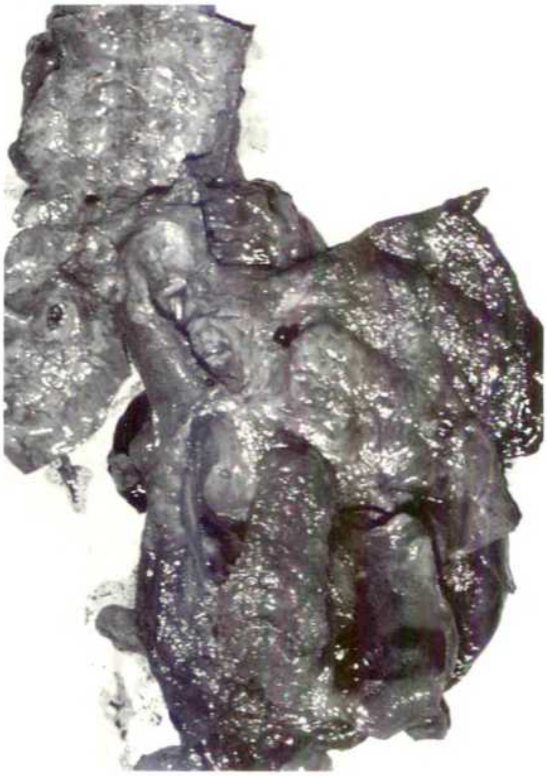
Case Report

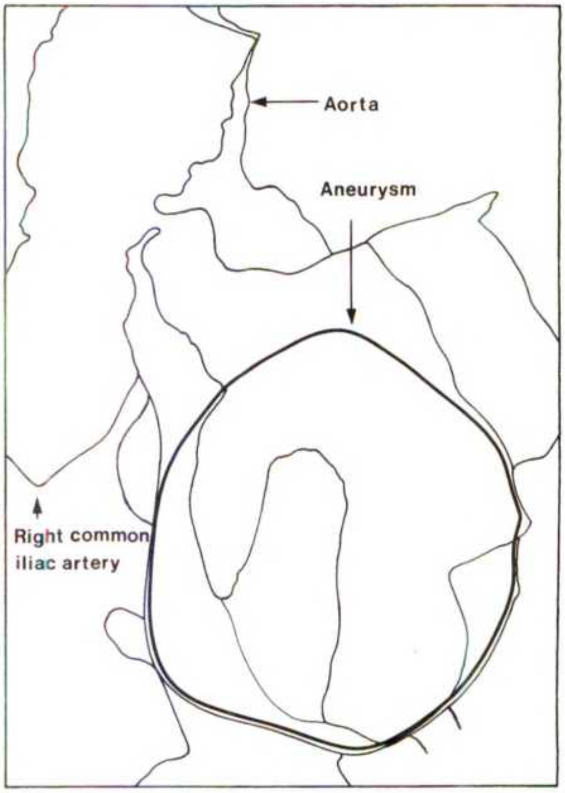
An 87-year-old man was admitted with a 1-week history of oliguria, low back pain and constipation. A large non-pulsatile mass, which was palpable both suprapubically and rectally, remained after urethral catheterisation. He passed 100 ml of urine over the next 24 h but plasma urea rose from 16.7 to 26 mmol/l. Ultrasound showed bilateral hydronephrosis, with a mass above and behind the bladder. Cystoscopy and sigmoidoscopy showed extrinsic compression of the bladder base and rectum. He collapsed and died before further investigations could be performed.

At post mortem the mass was found to be a 16 × 11 cm aneurysm of the left common and internal iliac arteries (Fig.). Extensive peri-aneurysmal haemorrhage had resulted in obstruction of both ureters. There was also a 5 × 3 cm right external iliac artery aneurysm.

Comment

Iliac artery aneurysms usually occur in elderly men presenting with rupture or symptoms from compression of adjacent structures (Schuler and Flanigan, 1982; McCready *et al.*, 1983). Ureteric involvement





is common but bilateral ureteric obstruction has rarely been reported.

Iliac artery aneurysms are difficult to diagnose; 28% are clinically impalpable (Schuler and Flanigan, 1982) but a rectal mass is palpable in 31% of internal iliac artery aneurysms; 72% of such palpable masses are pulsatile (Marino *et al.*, 1987).

Proctoscopy, cystoscopy and plain abdominal X-ray are of little use diagnostically (Schuler and Flanigan, 1982), although urography and retrograde ureterography may help. Angiography is specific (Schuler and Flanigan, 1982) and is best preceded by CT scan and ultrasound (McCready *et al.*, 1983). Early elective surgery has a low mortality but death is likely if the correct diagnosis is not made initially (Schuler and Flanigan, 1982).

A pelvic mass which persists after catheterisation should be investigated urgently to exclude iliac artery aneurysm.

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Selective Colonisation of a Urinary Catheter

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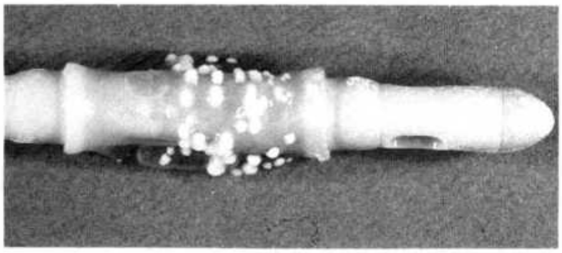
Silicone has been developed as the material of choice for long-term urinary catheters. It is claimed to be less tissue reactive, less liable to encrustation on the eyelet, lumen and balloon, and does not support bacterial or fungal growth (Binder and Gorick, 1969). Catheters are available as either silicone elastomer coated rubber or all silicone rubber. The coated catheters may be liable to peeling of the silicone layer on inflation of the balloon but the all-silicone catheter should be less liable to this potential colonisation site. We report



a case of candiduria following systemic antibiotic therapy in which large colonies of *Candida albicans* were observed macroscopically adhering and growing on the balloon section only of an all-silicone Foley catheter.

Case Report

An 83-year-old man was admitted with a stroke, as a result of which he became incontinent of urine and faeces. A latex Foley catheter was inserted into the bladder 3 days after admission and the patient was commenced on cefotaxime 2 g *bd* to treat a chest infection. There was no growth from a urine specimen taken at this time. Nine days later the antibiotic was stopped and the bladder catheter was replaced by an all-silicone elastomer 16 F Foley catheter (Simpla Plastics Ltd, UK). The balloon was inflated with 5 ml sterile water. This catheter was removed 6 weeks later and macroscopic colonies of *Candida albicans* were seen adherent to only the balloon section of the catheter (Fig.). The growth was in the form of multiple firm colonies very strongly attached to the balloon material. There was no crystal component to the colonies as investigated by histological section.

Comment

In our experience this was an ususual presentation of microbial adherence to urinary catheter material. The balloon section, which is made of the same material as the rest of the catheter (personal communication), clearly provides a preferential base for adherence of candida. There is no obvious reason for suggesting that this particular brand is at special risk of such colonisation and any silicone catheter balloon is possibly at equal risk. As can be seen from the Figure, it is primarily the distal two-thirds of the balloon which have the predominant growth, suggesting that the yeast was directed to this part by the presence of residual urine and gravity in the erect patient. The lower one-third would not be reached due to this section being in very close contact with the urethral orifice of the bladder. The stretching and thinning of the inflated all-silicone balloon may be an additional factor aiding colonisation, perhaps by allowing diffusion of nutrients for fungal growth.

While the selection of candida by antibacterial agents in the bladder is well recognised, the preferential colonisation of the balloon only is unusual, particularly in an all-silicone catheter. These observations may be of value in future catheter design and development.

Reference

Binder, C. A. and Gorick, P. (1969). Experience with silicone rubber-coated Foley urethral catheters. *J. Urol.*, **101**, 716–718.

Requests for reprints to: P. G. Murphy, Department of Bacteriology, Belfast City Hospital, Lisburn Road, Belfast BT9 7AD.

Atypical Presentation of Tuberculosis following Long-term Haemodialysis

N. D. HEATON, A. SEVERN and J. A. RENNIE, *Department of Surgery, South Dulwich Hospital, London*

Tuberculosis in the indigenous population of the United Kingdom is becoming rare except in high risk groups which include the immunocompromised, the elderly, alcoholics and vagrants. A patient on long-term haemodialysis with persistent anaemia and weight loss was eventually found to have extra-pulmonary tuberculosis. These patients have an increased risk of tuberculosis which may present atypically.

Case Report

A 69-year-old Caucasian woman presented with unexplained weight loss and persistent anaemia after 12 years of haemodialysis. Chronic renal failure had resulted from recurrent infection after ureterosigmoidostomy for bladder necrosis secondary to radiotherapy for carcinoma of the cervix in 1952. There were no specific symptoms apart from angina precipitated by the anaemia. Physical examination was otherwise normal. The haemoglobin was 6 g/dl with a normocytic, normochromic picture. Chest and abdominal X-rays, abdominal and pelvic ultrasound scans and CT scan of the chest and abdomen were normal. Barium enema and colonoscopy excluded colonic adenocarcinoma secondary to the ureterosigmoidostomy.

She developed right groin pain exacerbated by movement which radiated down the medial aspect of the thigh and also a 4 × 3 cm firm, fixed and non-tender mass in the right groin. Ultrasound scan showed a necrotic mass, possibly of lymph node origin, displacing the femoral artery and CT scan revealed a psoas abscess (Fig.). The

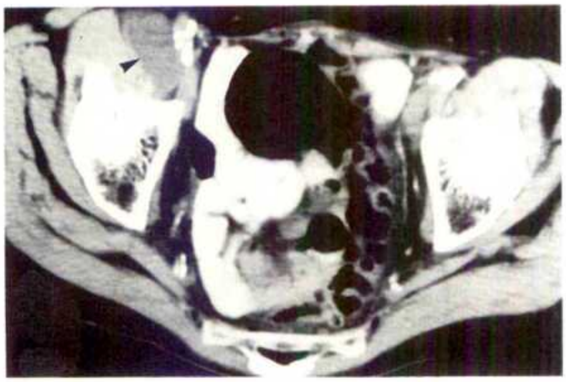


Fig. CT scan of the pelvis showing the right psoas abscess (arrow).

swelling in the groin was explored, yellow viscid fluid drained and the associated mass excised.

Histology revealed a mild non-specific chronic inflammatory exudate with large quantities of eosinophilic material which stained positively for amyloid and a giant cell reaction. Bacteriological cultures for *Mycobacterium tuberculosis* were positive. There had been tuberculosis in the family 30 years previously.

Comment

The incidence of tuberculosis in patients on long-term haemodialysis may be up to 12 times greater than that in the general population (Andrews *et al*., 1980). This is probably a reflection of impaired cellular immune function secondary to chronic renal failure. Patients with chronic renal impairment are at least 10 times more likely to contract tuberculosis than other members of the population.

Patients usually respond well to standard therapeutic antituberculous regimes, although the mycobacterium in this patient was resistant to streptomycin and isoniazid. Excretion of antituberculous drugs may be modified by dialysis (Urbanczik, 1983). Following treatment with isoniazid, rifampicin and pyrazinamide the patient is well. Retrospective review of the first CT scan revealed early changes of a psoas abscess that were not recognised.

A diagnosis of tuberculosis should be considered in patients on long-term haemodialysis presenting with non-specific symptoms such as weight loss, lethargy and anaemia despite a normal chest X-ray.

Acknowledgements

We thank Dr D. Taube for permission to report his patient, Dr M. Michell for providing the CT scan, and Mr M Yates for his help.

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Requests for reprints to: N. D. Heaton, Department of Surgery, South Dulwich Hospital, East Dulwich Grove, East Dulwich, London SE22 8PT.

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Points of Technique

Pharmacological Management of Erections during Transurethral Surgery

T. A. McNICHOLAS, K. THOMSON, H. S. ROGERS and J. P. BLANDY, *Departments of Urology and Anaesthetics, St Peter's Hospital and the London Hospital, London*

Patients who develop an erection during the course of transurethral surgery pose a challenge to the urologist. At the very least the procedure must be prolonged whilst waiting for the erection to subside. To persevere with resection during the erection risks causing sphincter damage because the landmarks become altered and displaced and bleeding obscures the view (Blandy, 1986). Surgery in such circumstances has medico-legal implications.

We have been unimpressed by traditional methods of counteracting erections during urological procedures such as achieving a deeper level of anaesthesia, the use of spinal or caudal blocks, the administration of beta blockers or ganglion blocking agents (*e.g.* trimethaphan or pentolinium) and the use of intravenous increments of benzodiazepines or ketamine.

Since none of these techniques has been shown to be clearly successful, we have recently used the intracavernosal injection of the alpha adrenoceptor stimulating drugs metaraminol and phenylephrine. In 6 recent cases where erections occurred during transurethral instrumentation and the erection failed to settle on deepening the level of anaesthesia, we injected 1 mg of phenylephrine or metaraminol into the cavernosal tissue. This resulted in each case in an almost immediate detumescence, allowing rapid resumption of the surgical procedure.

In most circumstances the endoscope should be removed from the urethra. We dilute the drug chosen with injection sodium chloride B.P. to achieve a dilution of 1 mg/ml of solution which is then injected into one of the cavernosal bodies using a 25G (orange) needle. The drug is then massaged throughout the penis.

The action of both drugs is rapid and detumescence is almost immediate. Both are associated with a degree of hypertension and should be given only with the agreement of the anaesthetist and after considering the anaesthetic agents being used and possible contra-indications such as pre-existing hypertension and cerebrovascular disease. The availability of automatic blood pressure monitoring devices ("Dinamap", Critikon) allows the frequent measurement of blood pressure and their use is recommended. If necessary, hypotensive treatment can be given by increasing the concentration of inhalational agent or by giving suitable doses of an alpha-blocker (*e.g.* phentolamine) or a peripheral vasodilator (*e.g.* hydrallazine).

In 3 patients given metaraminol the mean blood pressure rise was 22/20 mm Hg (systolic/diastolic) with a peak 11 min after injection. Blood pressure returned to pre-treatment levels by 28 min without further pharmacological manipulation. Recordings in 1 patient given phenylephrine showed a peak rise of blood pressure of 70/60 mm Hg approximately 4 min after injection. Blood pressure returned to pre-treatment levels by 22 min.

Considering the importance of the problem there is little guidance on the management of erections complicating urological surgery. Gale (1972) described the use of intravenous ketamine to abolish erections during penile surgery. Excitement and delirium may occur in the conscious patient and therefore it should only be considered for patients under general anaesthesia. Benzon *et al.* (1983) found that ketamine caused a delayed detumescence that was of little surgical use and was also associated with significantly raised blood pressure. We have not been impressed with its use. De Meyer and De Sy (1986) reported the use of small doses of intracavernosal nor-adrenaline, which caused quick detumescence with no post-operative sequelae in a group of 17 patients with peri-operative erections. This agent is less frequently available than metaraminol and may result in more marked and undesirable local vasoconstriction.

During experiments on the treatment of erectile impotence by cavernosal alpha blockade, Brindley (1984) found that the tumescent effect could be reversed by the intracavernosal injection of metaraminol. He described only minor side effects and did not mention hypertension. However, careful monitoring of blood pressure is required as any leakage of the drug from the penis into the systemic circulation is accompanied by a degree of hypertension, as seen in our patients.

Phenylephrine has been proposed as the drug of choice, although it also causes hypertension, because it may have a less prolonged vasoconstrictor effect (unpublished data). Metaraminol and phenylephrine should be available for the pharmacological reversal of erections complicating transurethral surgery.

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Requests for reprints to: T. A. McNicholas, St Paul's Hospital, 24 Endell Street, London WC2H 9AE.

Transrectal Prostatic Biopsy in Genucubital Position

D. YACHIA, D. LASK and M. FRIEDMAN, *Department of Urology, Hillel Yaffe Memorial Hospital, Hadera, Israel*

Since the transrectal route for prostatic biopsy was described in 1937, it has become an accepted procedure for diagnosing prostatic malignancy and no treatment should be started without histological confirmation.

Transrectal biopsy is usually taken with the patient in the simple or exaggerated lithotomy position, although some British urologists take the biopsy with the patient in the left lateral position (Hendry and Williams, 1971). We present our experience of 90 transrectal prostatic core biopsies performed with the patient in the genucubital (knee-chest) position.

Patients are given a Fleet-Enema to reduce rectal contents and take a shower before the procedure. They are put in the knee-chest position at the edge of the operating table. The prostate is palpated and the suspected area reassessed. The gluteal and anal areas are scrubbed with povidone iodine and the patient is draped with sterile sheets. About 5 ml of povidone iodine ointment is taken on to the index finger and the Tru-Cut biopsy needle is embedded in it. The finger is inserted, the needle directed to the suspected site, and the biopsy taken. Afterwards the prostate is smeared with a layer of the same ointment. This position provides an easier approach to the prostate, gives greater accuracy in taking the biopsy, and prevents unnecessary cervical and back pain for the surgeon.

Reference

Hendry, W. F. and Williams, J. P. (1971). Transrectal prostatic biopsy. *Br. Med. J.*, **4**, 595–597.

Requests for reprints to: D. Yachia, Department of Urology, Hillel Yaffe Memorial Hospital, Hadera 38101, Israel.

Arteriocaliceal Fistula Controlled by Trans-catheter Occlusion

M. J. STOWER, M. G. WYATT and W. D. JEANS, *Departments of Urology and Radiology, Royal Infirmary, Bristol*

Case Report

A 45-year-old male was admitted 12 h after he had fallen down stairs whilst intoxicated. He was complaining of right loin pain, with haematuria. Excretion urography showed extravasation of contrast from a lower pole calix with rapid pooling of contrast in the renal pelvis. He was

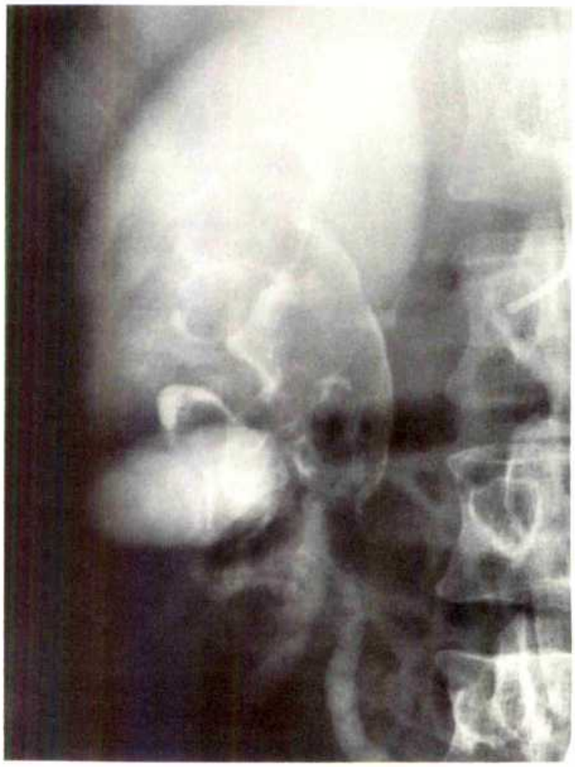

Fig. 1 Late film from arteriogram showing contrast pooling in renal tear, staining of clot in the renal pelvis and rapid opacification of the ureter.

treated conservatively and discharged symptom-free on the eighth day.

Twelve days later he returned with massive haematuria, having been on another drinking spree. He was hypotensive and required transfusion. Urography showed blood clot in both the right renal pelvis and the bladder. An arteriogram showed a single lower pole renal artery with filling of a cavity from which contrast medium passed rapidly into the renal pelvis and down the ureter (Fig. 1). The lower pole artery was occluded with a distal Gian Turco wire coil and gelfoam proximally. A post-embolisation film showed no flow into the cavity (Fig. 2). The haematuria settled and he discharged himself 6 days later.

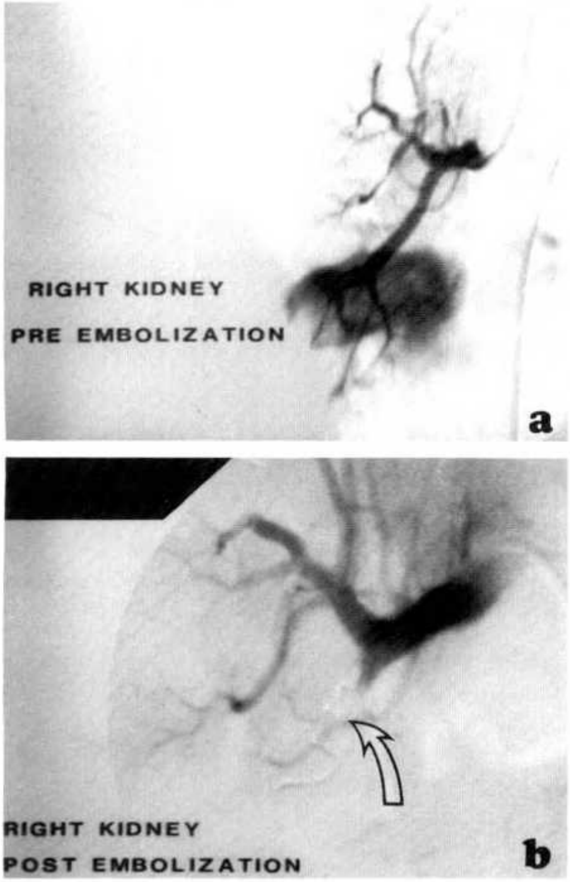

Fig. 2 Digital subtraction films showing (A) single lower pole artery and contrast medium in renal tear, before embolisation, and (B) Gian Turco coil (arrow) in occluded lower pole artery, after embolisation.

Comment

The recurrent haematuria and hypotension in our patient could have been an indication for surgery which might have resulted in nephrectomy. Transcatheter occlusion has a high success rate (Uflacker *et al.*, 1984) and should be tried first (White, 1976). Arteriocaliceal fistulae are rare but have been treated by occlusion previously (Blackwell *et al.*, 1978).

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Requests for reprints to: M. J. Stower, Department of Urology, Level 5, Bristol Royal Infirmary, Bristol BS2 8HW.

British Journal of Urology (1989), **64**, 438–439
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Correspondence

Dear Sir,

re **Duplex scanning in suspected vasculogenic impotence: a worthwhile exercise?** L. Q. Robinson *et al.* *Br. J. Urol.*, **63**, 432–436, 1989.

We agree with Robinson *et al.* that the PBI is unreliable in the investigation of penile arterial insufficiency. We are currently also attempting to measure penile blood flow after papaverine as an alternative to the PBI but unlike the authors we are using isotopic methods of estimating blood flow. A recurring difficulty with such studies is that there is no accepted standard by which such studies can be evaluated; arteriography does not give a functional assessment of arterial supply and the demonstration of venous leakage by cavernosography does not exclude significant arterial insufficiency; indeed, as the authors themselves have stated, there may actually be a causal relationship between the two.

The authors used the test under assessment to direct subsequent investigations and then used the results of these subsequent investigations to support the validity of the test; the conclusions reached by such methodology must remain in doubt. Patients who did not achieve erection with papaverine and in whom the penile artery peak velocity increase and deep artery diameter increase were low were classified as having arterial disease. This combination could have occurred in normals with relative insensitivity to papaverine or in those venous leakers in whom the papaverine rapidly entered the systemic circulation, thereby not only failing to affect the penile arteries but also possibly causing systemic hypotension. On the basis of the test, venous leakage was assumed to be absent in 92 of the 109 patients who failed to respond fully to papaverine, although confirmation by cavernosography was obtained in only 3 of these. Conversely, in the 16 patients in whom venous leakage was demonstrated there was no evidence, apart from the duplex scan, that they did not also have arterial disease.

Duplex scanning may yet prove to be a useful indicator of arterial insufficiency in the investigation of impotence but cannot be used to exclude venous leakage as the authors appear to have done. This may explain the low incidence of venous leakage in this study.

Yours sincerely,

P. Grech, D. A. Cunningham and R. O'N. Witherow
Departments of Clinical Physics and Urology,
St Mary's Hospital, Praed Street, London W2 1NY.

Reply by L. Q. Robinson. In reply to Dr Grech's letter I wish to make the following comments. There is no doubt from the study that duplex scanning is an objective assessment of the individual penile vascular reaction, and a "threshold value" in the deep arteries is required. Venous leakage was not assumed to be absent in those not responding fully to papaverine, but as venous surgery seems to be more likely to succeed in those with a good arterial inflow but poor erections, only in this latter group of patients was cavernosography performed. It would indeed have been interesting to perform venous studies on all of the patients, but the therapeutic benefit would probably have been minimal. It was not our intention to validate duplex scanning with cavernosography, but rather to use the latter investigation in a more therapeutically orientated manner. Duplex scanning was therefore not used to exclude venous leakage, and we would quite agree that some patients may have dual pathology. However, until revascularisation becomes reliable we believe the application of cavernosography should be selective.

The comment regarding the relative insensitivity of some patients to papaverine obviously pertains to all studies, and although not mentioned in the article, to reduce systemic absorption, all patients had an elastic band placed at the base of the penis before, and for 2 minutes following, injection.

Dear Sir,

re **Near-fatal urinary peritonitis secondary to ureteric calculus.** E. C. Paraskevaides and M. Cooper Wilson. *Br. J. Urol.*, **63**, 437–438, 1989.

This was an interesting Case Report but it provides a timely stimulus to put away once and for all the traditional advice for patients with ureteric calculi to drink plenty to help wash away the stone or be "encouraged to drink clear fluids", as reported here.

In the early stages of acute obstructive uropathy, renal blood flow is preserved or transiently increased; renal function is not impaired but excretion is blocked. Under such circumstances, diuresis rapidly fills the collecting system with urine which is unable to leave via the ureter and may lead to extravasation from small tears in the caliceal fornices, which is seen not infrequently on urography in acute uteric colic from even mild contrast-induced diuresis. This can lead to urinoma formation as urine trapped within Gerota's fascia tracks inferiorly and anteriorly towards the iliac fossa or perforates into the peritoneum, as in this case.

On the other hand, if obstruction becomes established without the above complications, renal blood flow and glomerular filtration rate will fall, the fluid load will be handled predominantly by the contralateral kidney and the extra fluids will have no effect on "washing out the stone". As ureteric dilatation increases (accelerated by any diuresis), peristalsis, the only propulsive force likely to help the onward passage of a stone, will become compromised and ineffective. If the patient is nauseous or vomiting these symptoms will be made worse by increased oral fluid. If prostaglandin synthetase inhibitors such as indomethacin are used for pain relief, they will be rendered ineffective by any form of diuresis. Diuresis can be encouraged after ESWL, where there is a need to wash out stone fragments through an *unobstructed* outflow tract from a functioning kidney. This situation is in no way comparable to the pathophysiological conditions pertaining during acute obstructive uropathy.

The management of ureteric colic should include adequate analgesia and anti-emetics, the maintenance of normal hydration by oral or intravenous fluids, the use where desired of prostaglandin synthetase inhibitors, antibiotics if necessary and constant supervision so that prompt urological intervention by percutaneous surgery, endourology or ESWL can be undertaken as soon as the risk/benefit ratio of conservative therapy becomes adverse. It should no longer include advice to drink excessive or copious amounts of fluids; having no sound physiological basis, such advice is at best pointless and at worst dangerous.

Yours sincerely,

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Stockport SK2 7JE.

British Journal of Urology (1989), 64, 440–441

Notices

British Association of Urological Surgeons

President: R. T. Turner-Warwick, DSc, DM, MCh, FRCP, FRCS, FACS

Annual Meeting. Scarborough. 10–13 July 1990

Abstracts of contributions to be considered as either papers, posters or videos by the Programme Sub-Committee of Council should be submitted on the special forms available from the BAUS Secretariat. Completed forms, which should state clearly whether the submission is a paper, a poster or a video, must be returned to the Honorary Secretary by Friday, 5 January 1990.

Abstracts not on the special forms will NOT be considered.

All correspondence to: M. G. Royle, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

Bard Award

This award, made possible by the generosity of C. R. Bard International Limited, was given for the first time at the Annual Meeting in Bristol in 1979. The award will consist of the sum of £1500 and the Bard Silver Medal. The award will be given for the best essay submitted specifically for consideration for the award by members of the Association (non-members must be sponsored by a Full Member).

Essays should be based on original work on any topic connected with urological surgery, either clinical or experimental. The essay should include a review of the literature and the clinical implications of the work performed. A panel of three adjudicators will be nominated at the February meeting of Council each year. Submissions for the award should be made in triplicate by 1 March to the Honorary Secretary. The winning essay will be read during the Annual Meeting and should not exceed 20 minutes' duration.

The Surgitek Prize

The Prize consists of a fully sponsored visit to the American Urological Association Annual Five-day Meeting, together with a tour of Surgitek's manufacturing facility in Racine, Wisconsin. It is open to trainees in urology and consultants who are within 5 years of first appointment. Entrants should submit a written paper, which may be on any subject, but must be unpublished, and must not have been submitted previously for the Surgitek Prize, or other prizes. The winning entry will be the one which is considered to be "The most significant contribution to urology".

Entries will be judged by three members of BAUS Council nominated at the October meeting of Council. Papers should be submitted in triplicate to the Honorary Secretary by 1 January each year.

Hans Marberger Prize

The Hans Marberger Prize will be awarded for the first time at the meeting of the German Urological Association in Hamburg in 1990. The prize, which will be donated by Karl Storz Ltd, will amount to öS 50,000 and will be awarded biennially for the best paper in the field of reconstructive surgery in urology or endourology. The award may be split.

Papers may be written in either German or English and should be submitted in triplicate to Dr H. Fuchshuber, Adamgasse 15, A-6020 Innsbruck, by 1 March 1990.

A code word should be affixed to each manuscript, which should not bear the author's name. In a separate envelope bearing the code word the following information should be given: author's first name, surname, position, and code word.

Early Prostatic Cancer—Which Treatment?

Newport, Gwent. 3 November 1989

Further information from: Mr W. B. Peeling, Department of Urology, St Woolos Hospital, Newport, Gwent NP9 4SZ.

Annual Meeting of the British Andrology Society

Edinburgh. 10 and 11 November 1989

Further information from: Dr C. Barrett, Department of Obstetrics and Gynaecology, University of Sheffield Medical School, Beech Hill Road, Sheffield S10 2RX, or Mr T. B. Hargreave, Department of Surgery (Urology), Western General Hospital, Edinburgh EH4 2XU.

Fourth Steglitz Pediatric Surgical Symposium: Laser Application in Children

Berlin, West Germany. 10 and 11 November 1989

Further information from: Dr Felix Schier, Department of Pediatric Surgery, Free University of Berlin, Hindenburgdamm 30, 1000 Berlin 45, West Germany.

Video Meeting on Pathology of the Urinary Tract in Children

Lyon, France. 19 and 20 January 1990

Further information from: Secrétariat du Congrès, Service d'Urologie Pédiatrique, Hôpital Debrousse, 29 rue Soeur Bouvier, 69322 Lyon Cedex 05, France.

Second European Symposium on Stone Disease

Basel, Switzerland. 22–24 March 1990

Further information from: Mrs W. Heinzelmann, Urologische Klinik, Departement Chirurgie der Universität Basel, Spitalstrasse 21, CH-4031 Basel, Switzerland.

Second Copenhagen Symposium on Uroradiology

Herlev, Denmark. 27–30 August 1990

The following topics will be included: Upper urinary tract imaging and intervention; Contrast medium nephrotoxicity; Hydronephrosis/obstruction; The urinary bladder; Genital radiology; The adrenal glands; Free communications.

International Continence Society: 20th Annual Meeting

Aarhus, Denmark. 12–15 September 1990

Further information from: Dr J. P. Nørgaard, Institute of Clinical Experimental Research, University of Aarhus, DK-8000 Aarhus C, Denmark.

British Journal of Urology (1989), 64, 442–443

Diary

1989

October 12–14	Urologic Oncology—Today and Tomorrow. University of Toronto. Contact Strategem Communications, 2 Sheppard Avenue East, Suite 604, Willowdate, Ontario M2N 5Y7, Canada. Tel: (416) 229 2331
October 21–23	Academy of Pediatrics, Urology Section Meeting, Chicago. Contact Edmund Gonzales, Dept of Pediatric Urology, 6621 Fannin St, Houston, Texas 77030. Tel: (713) 798 1560.
October 23–24	21st RCOG Study Group on Micturition. Royal College of Obstetricians and Gynaecologists, London. Contact Mr J O Drife, RCOG, Regents Park, London WC1. Tel: 01 262 5425
October 25–27	Advanced Stone Management Course, Institute of Urology. Contact Course Secretariat, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01 240 9115
November 16–17 (SR)	**Renal Failure and Transplantation** **Institute of Urology. Contact Course Secretariat, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01 240 9115**
November 20 (SR)	**BAUS Instrument Day—Lasers in Urology** **Royal College of Surgeons, London. Contact BAUS Secretariat. Tel: 01 405 1390**
November 24–25	**International Meeting on Sacral Anterior Root Stimulators—Le Mans. Contact Professor Brindley, The Maudesley Hospital, London. Tel: 01 703 8458**
November 27–29 (SR)	**Endoscopic Application of Lasers—Institute of Urology and University College, London. Contact Course Secretariat, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01 240 9115**

1990

January 5	**Closing Date for submission of BAUS abstracts**
January 8– February 2	**Block 2 Diploma Course, Institute of Urology. Contact Course Secretariat, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01 240 9115**
January 12 (SR)	**Guy's Research Meeting—Roden's Suite, Guy's Hospital, London. Details from Mr A R Mundy, Department of Urology, Guy's Hospital, London SE1 9RT. Tel: 01 407 7600**
January 27– February 3	1990 Winter Urologic Forum Meeting Steamboat Springs, Colorado, USA. Contact Linda Mace, Staff Assistant, Box 3707, Duke Medical Center, Durham, NC 27710, USA.
March 28–30	**Association of Surgeons of Great Britain and Ireland. Annual Meeting. Cardiff. Closing dates for abstracts 7th October 1989. Contact Ms Caroline Ross at the Royal College of Surgeons, Lincolns Inn Fields, London WC1. Tel: 01 405 3474**

May 13–17	**Annual Meeting of the American Urological Association, New Orleans. Contact The Secretary, AUA, 1120 N Charles Street, Baltimore, Maryland 21201, USA.**
May 27–June 3	Urological Society of Australasia. 43rd Annual Scientific Meeting Darwin–Kakadu. Contact ASM Secretariat, Urological Society of Australasia, 145 MacQuarie St, Sydney 2000, Australia. Tel: 27 4461
June 13–16	Ninth Congress of the European Association of Urology. Amsterdam. Contact QLT Convention Services, Keizersgracht 792, 1017 AC Amsterdam, The Netherlands. Tel: 010 31 20261372
June 24–28	Canadian Urological Association Meeting, Vancouver, British Columbia, Canada. Contact Dr J. P. Collins, Ottawa Civic Hospital, 1053 Carling Avenue, Ottawa, Ontario K1Y 4E9, Canada.
July 10–13	BAUS Annual Meeting, Spa Conference Centre, Scarborough. Contact Secretariat, Royal College of Surgeons, Lincolns Inn Fields, London WC1. Tel: 01 405 1390

Courses which are recommended for Senior Registrar Education are marked with (SR).

All 'BAUS–associated' meetings/courses are printed in bold.

British Journal of Urology (1989), **64**, 444

0007-1331/89/0064-0444/$10 00

Book Reviews

Ureteroscopy. By J. L. Huffman, D. H. Bagley and E. S. Lyon. Pp. vi+201. Philadelphia, London, Toronto, Montreal, Sydney, Tokyo: Saunders. 1988. Price £28.50.

This book aims to discuss the instruments, indications and techniques for ureteroscopy for the novice as well as the established practitioner. It is divided into 12 chapters covering the history of the development of the ureteroscope, indications, anatomy, patient preparation, dilatation of the ureter and descriptions of the actual procedures of stone removal and tumour resection. Post-operative care and complications as well as instrument care are subsequently discussed. An appendix covers a problem-orientated approach to the hazards of uretero-pyeloscopy.

The book is well set out with clear text, mostly good X-ray illustrations and excellent line drawings. The text, however, does tend to be repetitive and at the end of the day the book does not provide a good perspective, particularly for the novice ureteroscopist The sections containing stone removal do not stress the importance of patient selection. The novice should limit his initial attempts at ureteroscopy to small, non-impacted stones in the distal ureter. Some of the earliest illustrations in the book show large, complicated stones or stones in the upper third of the ureter which are only suitable for removal by the most experienced practitioner. The emphasis on transitional cell carcinoma of the upper tract is also misplaced. The impression given by this book is that all upper tract tumours should be assessed by ureteroscopy. Clearly this is not practical and ureteroscopic assessment should be reserved for those cases where other standard imaging techniques have proved equivocal. Ureteroscopy is an invasive procedure and it is possible to compromise subsequent surgery. The concept of "tumour mapping" with a rigid ureteroscope seems rather academic.

The problem-orientated approach to the hazards of uretero-pyeloscopy mentions the important subject of follow-up after this procedure but does not mention the use of cystograms to identify reflux or enter into any meaningful discussion about aetiology, prevention or management of ureteric strictures

Ureteroscopy is now a commonly performed urological procedure. It would be difficult to imagine managing upper tract stone disease without this instrument There is, therefore, a need for an authoritative reference on this subject. Unfortunately, this book fails to fill the gap completely.

Overcoming Urinary Incontinence. A Simple Self-help Guide. By R. J. Millard. Pp. xiii+109. Wellingborough: Thorsons Publishers Ltd. 1987. Price £4.99.

The taboo surrounding discussion of urinary incontinence still prevails, but books such as this offer some practical and emotional support to sufferers. A relative to whom I lent it found the sympathetic and commonsense approach reassuring and has undoubtedly been helped simply by concentrating her mind on the problem. She has kept the book and has embarked with enthusiasm on the somewhat formidable programme of exercises and behavioural approaches described. However, she had to read the anatomical and functional descriptions several times before they began to make sense.

There is no substitute for sensitive, professional help, and no individual book can adopt the right approach for all readers. Dr Millard's book is, however, a valuable supplement and helps to fill a gap in the currently sparse choice of consumer-orientated literature on this subject.

Oxalate Metabolism in Relation to Urinary Stone. Edited by G. A. Rose. Pp. xvi+197. London, Berlin, Heidelberg, New York, Paris, Tokyo: Springer-Verlag. 1988. Price £48.00.

This little book is a remarkable combination of science and personal experience. To biochemists it should have instant appeal because of the thorough analysis of the methodology involved in measuring a substance as fickle as urinary oxalate. To the modern clinician—urologist or renal physician—the book gives valuable information essential to the understanding of stone disease, a condition which can cause problems to a most important socio-economic group in society. Among many ideas presented it is intriguing to consider the significance of "mild unstable hyperoxaluria" and for those interested in the therapeutic, long-term management of stone patients the chapter on pyridoxine metabolism is fascinating.

Throughout the book there are many ideas and concepts which should stimulate further research and study. The diagrams and scientific tables are well presented and the bibliography is extensive. The editor's knowledge and fascination with this topic are presented with an unusual combination of scientific knowledge and intellectual honesty which make this little volume particularly valuable and readable The strong personal touch is very obvious and to have as an editor a recognised world authority should make this book essential reading to the staff in all modern urological departments.

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REVIEW

A Chemist's View of the History of Urinary Stone Analysis

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The history of stone analysis, like that of chemistry itself, has proceeded spasmodically. At times, progress has been the result of bitter controversy, at others, research has been diverted into blind alleys. To complicate matters still further, the sites and the composition of stones have changed over the past 400 years. To the founder members of the Royal Society, all stones were bladder stones and they tended to be much larger than those encountered today. Moreover, their chemical composition reflected the eating habits of a time very different from our own.

The number of stones available for study depended largely on the number of lithotomies but mediaeval medicine was opposed to lithotomy on Hippocratic, canonical and pragmatic grounds. Cutting for stone dates from Saxon times in England and was usually performed by itinerant folk-surgeons, often as a side-line to their main occupation of hog-gelding. Stones were not investigated but revered as talismans or objects of magic. Most prized of all were the bezoar stones, concentrations of calculous material found in the alimentary tracts of animals, especially Iranian mountain goats. In a paper submitted to the Museum of Natural History in Paris, Fourcroy and Vauquelin (1802) demonstrated that these objects were composed of magnesium ammonium phosphate.

The study of human stones depended on the existence of a safe and simple method of lithotomy and a nucleus of natural scientists willing to challenge existing notions of the composition of matter. In England such a nucleus existed in the Royal Society of London, which received added status following an official inauguration in 1660. Although its early transactions were devoted to the exhibition and collection of curiosities rather than systematic science, it constituted a forum in which ideas and facts could be exchanged. One of the most inquisitive of its founder members was its royal patron, Charles II, who in 1662, on a visit to Newmarket races, was shown the current curiosity, a stone weighing over 2 lb removed from a woman in Bury St Edmunds. This calculus was cut across to show the king its annular internal structure.

The two greatest pioneers of modern medicine, Thomas Sydenham (1624–1689) and Herman Boerhaave (1668–1738) suffered from both gout and "the stone". These diseases so often occurred together that it was believed that stones were merely a symptom of gout, a clinical condition first defined from personal experience in a classic description by Sydenham (1683). Since the two most eminent physicians of the day could not cure themselves of uric acid lithiasis, it is not surprising that there was little hope for their patients, who turned either to surgeons or to fringe medicine. It was left to an unauthorised practitioner to concoct a remedy for stones that stimulated the first phase of scientific research into their composition.

The point at issue was not to determine the composition of stones but to discover an agent which would dissolve them. The treatment which seemed most effective was soap and the most popular formulation was marketed by an unqualified druggist, Joanna Stephens. Mrs Stephens was financially astute and succeeded in selling the patent of her medicine to Parliament for £5000, due largely to the fact that both "houses" were packed with her customers.

The scientific controversy over her nostrum revolved around the central question of whether it could reverse the growth of stones in the bladder. With hindsight, it is easy to understand why her

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treatment worked. The ingestion of large quantities of soap produces a very alkaline urine which will, in time, dissolve stones consisting of uric acid or urates. In 1745, when Mrs Stephens made her financial coup, the stone population consisted largely of this chemical type. Some scientists supported her claim whilst others argued on theoretical grounds that alkali was not the correct solvent. There was, however, another reason for the rejection of Mrs Stephens' theories: she was a woman and not qualified in any of the three medical or paramedical professions; she was neither physician, surgeon nor apothecary.

One of the strongest attacks on the Stephens camp was made by Dr Henry Bracken, a pupil of Boerhaave who regarded his master as infallible. Although Bracken did not perform any experimental work to justify his opposition, he did offer a theory of stone composition which was incompatible with the idea of alkali-soluble calculi. He maintained that stones were "tartar", like the "fur" in kettles or, in present parlance, like the scale that dentists remove from neglected teeth (Bracken, 1739). Tartar was deposited in layers and this would explain the appearance of the stone that had been shown to Charles II at Bury St Edmunds. Tartar was a chalky substance so the best solvent should, logically, be an acid. Another believer in the tartar theory was Stephen Hales (1677–1761), an amateur scientist in holy orders and priest in charge of the parish of Teddington in Middlesex. He discovered that many stones emitted what he called "elastic air" when treated with acid which confirmed their chalky nature (Hales, 1740). In fact, the carbon dioxide production he observed derived from the carbonate-apatite complex present in those stones associated with recurrent urinary tract infection. Hales argued that the solvent should not be administered orally but applied as a bladder wash. The reagent he used was oil of vitriol (dilute sulphuric acid) but he was discouraged by the inability of experimental animals (his pet dogs) to withstand this draconian treatment. In 1745, he claimed a modest success when he read a paper to the Royal Society on his "Proposal to bring small passable stones soon and with ease out of the bladder". What he seems to have done is to have assisted the passage of calculi which would have eventually passed naturally.

The "elastic air" of Hales became the "fixed air" of Joseph Black (1728–1799). He intended to enter the lithotriptic controversy on the side of the tartar faction but was sidetracked in 1751 into work of the greatest importance on the carbonates of calcium and magnesium. His analyses were quantitative and years ahead of their time.

The tartar school believed that stones were made of what might, in more modern terms, be called alkaline earths; opponents believed that stones, to be soluble in alkali, must consist of an acid-like substance, although they lacked the necessary language to express this in words. The experimental work to support this hypothesis was performed by David Hartley (1705–1757). His position was made suspect by the fact that he was an acknowledged champion and patient of Mrs Stephens. He investigated the solvent effect of her formula by dosing himself with it until his urine was strongly alkaline; he then immersed pre-weighed stones in his own urine and reassessed their weight over a prolonged period. An indicator (syrup of violets) was used to ensure that the alkalinity of the urine was maintained and the majority of the stones did lose weight. From these observations, Hartley (1739) argued not that the soap concoction could reverse the formation of bladder stone but that it should be taken regularly as a prophylactic. He was supported in this belief by a Parliamentary Commission investigating Mrs Stephens' claim.

When, in 1776, Carl Wilhelm Scheele (1742–1786) discovered uric acid in stones, he promptly named it "lithic acid". Scheele was a Swedish apothecary from the Hanseatic League town of Stralsund on the southern shore of the Baltic; this is now part of the German Democratic Republic and some of his biographers have proclaimed him as a great German scientist, although his links were predominantly with Swedish centres of learning at Uppsala and Gothenburg. His work on stones appeared to vindicate that of Hartley and the association between stones and gout was proved experimentally when Garrod (1854) demonstrated, using the murexide test, that uric acid was also present in the blood. Throughout the last quarter of the eighteenth century, stones ceased to be a subject of great general interest but a handful of men were destined to make discoveries which put Scheele's findings into perspective.

The so-called hempseed and mulberry stones (the "mulberry" being in fact a cluster of "hempseeds") did not accord with accepted theories of the time. If these comprised a different form of "lithic acid", why did they behave differently, exhibiting different solubility characteristics and leaving an ash on burning and, most curious of all, why was this ash calcium oxide? Starting with these inexplicable findings, William Hyde Wollaston (1776–1828) was able to demolish the single-constituent theory of stone composition. In a classic paper to the Royal Society in 1797, not only was he able to demonstrate the existence of stones consisting of "oxalate of lime" but he also discovered the existence of stones consisting of "phosphate of lime and magnesium". In 1810 he went further and described a new stone constituent, cystic oxide (or cystine), the name suggested by Berzelius in 1833. He was at a loss to describe the odour of cystine burning as he knew "no smell which it can be said to resemble".

Similar research was being pursued in post-revolutionary Paris. The leading French biochemist of the period, Antoine de Fourcroy (1755–1809), owed his survival, at a time when fellow-scientists like Lavoisier were being guillotined, to his political activities in the cause of the new regime. As a scientist his greatest achievement was the isolation of urea from urine and other body fluids. With his assistant Vauquelin he confirmed Wollaston's findings regarding the variety of stone constituents. However, Fourcroy's main interest was in the calculi which contained the ammonium radical and, in particular, triple phosphate stones. He had already identified this substance in bezoar stones from the stomachs of wild goats and speculated that the stones from both goats and humans were associated with the fermentation of urea. Considering the vague and often erroneous ideas of enzymology and bacterial action then current, this was a bold and brilliant insight which was later to be fully vindicated.

In a few years Wollaston and Fourcroy took qualitative stone analysis almost as far as it could go but their disciples expanded the methods into a system. In 1817, Alexander Marcet wrote a textbook on "The chemical history . . . of calculous disorders" which contained a methodological section with drawings of the necessary apparatus. The French equivalent of Marcet's book, by François Magendie (1818), was curiously old-fashioned; 100 of its 116 pages were devoted to uric acid stones.

The last of the great stone analysers was John Yelloly (1774–1842), a Norwich physician and, in terms of the number of stones analysed, the busiest of them all. He made a collection of 649 stones, principally from the Royal Norfolk Hospital but with contributions from Guy's and the Hunterian Museum. His technique was to sample stones from the centre outwards and he showed that many stones were of a mixed or layered composition (Yelloly, 1830). Assisting him were two very able technicians, William Prout and Michael Faraday of the Royal Institution. With their help he identified virtually all of the anomalous substances in his samples, including a very rare case of a stone partially composed of silica. Of greater significance, however, was the painstaking statistical analysis of his sample. He showed that while uric acid stones predominated in the population, a distinction should be made between uric acid stones from adults and ammonium urate stones from children; although he did not understand why children developed stones, he knew that they did not suffer from gout.

Those who did take the trouble to analyse calculi at this time did so out of scientific curiosity and not with any intention of modifying the patient's treatment. In any event the patient was cured in the sense that he had been "cut for the stone". However, the laboratory notes on such calculi represent some of the earliest clinical pathology reports and, despite differences in terminology, reveal more to the informed modern reader than they did to clinicians of the time. An example of this was recently discovered in the archives of the pathology museum at the Royal Berkshire Hospital. An unknown analyst had discovered, in various parts of a stone, lithic acid, lithate of ammonia, ammoniacomagnesic crystals and phosphate of lime, suggesting a medical history of early phosphate deficiency superseded in later life by gout and urinary tract infection.

The crystalline nature of many stones determined the next phase in the history of stone analysis. The home of mineralogy in England was Cambridge, where research was presided over by the formidable figure of William Whewell (1794–1866) who, in 1838, relinquished the chair of Mineralogy for that of Moral Theology. In 1828 he had produced his principal scientific text, the "Essay on Mineralogical Classification and Nomenclature", which made his subject independent of chemistry. The crystalline substances in stones were minerals and, over the course of the next century, many of them were found in mineralogical sites even though they were almost invariably artefacts of mammalian excretion in the remote past. This meant that in accordance with Whewell's rules, all inorganic stone constituents had to be "rechristened". No one pointed out to Whewell that this would lead to a rift between mineralogy and chemistry, so when, in 1852, his erstwhile student at Cambridge, William Hallowes Miller (1801–1880), discovered the monohydrate of "oxalate of lime" in organic deposits of great antiquity, the name Whewellite was conferred on the rediscovered substance, in honour of the pioneer of this branch of science. This was not the first stone constituent to be renamed. "Apatite" was found in a similar site by Werner as early as 1788; this name came to be used for a whole group of complex "phosphates of lime". In 1845 struvite was found by Ulex in a stratum of dung under a demolished church in Hamburg; it was named, somewhat inconsequentially, after a Russian diplomat, Baron von Struve. Brushite, originally termed epiglaubite, was discovered in similar deposits on a Caribbean island by Shepard in 1856. Perhaps the most bizarre site for such a find was a cave filled with bat guano at Ballarat where, in 1879, whilst searching for precious minerals, Von Rath discovered the rare stone constituent, Newberyite, which results from magnesium ammonium phosphate being stripped of its ammonia. In the hope of obtaining a mining concession, the German geologist named it after a local politician.

To complete this catalogue of names, it is necessary to acknowledge the work of Clifford Frondel from Harvard University. In 1941 he found another phosphate, whitlockite, in once-inhabited caves and in hydrothermal deposits. In 1942 weddelite was isolated in single crystals from mud dredged out of the Weddel Sea in the Antarctic. It is symptomatic of the rift between chemistry and mineral crystallography at this time that while chemists were well aware of 2 different forms of calcium oxalate in stones prior to 1941 (Nakano, 1922), the dihydrate crystal had not been "officially" discovered.

Before 1913, crystal studies relied to a large extent on light microscopy but, in that year, Sir William (W. H.) Bragg (1862–1942) and his son, W. L. Bragg, began to use X-ray diffraction methods to study crystal lattice structure. This rapidly developed into a means of analysing crystalline substances qualitatively and, eventually, semiquantitatively. At first this remained a research tool but in the ensuing period many useful applications were found, especially in the field of metallurgy. Frondel was one of the first to apply crystallography to stone research, in association with E. L. Prien (Prien and Frondel, 1947). In the United States, crystallographic analysis of calculi took off on a grand scale and Herring (1962) examined over 10,000 stones. In Britain, the pioneers were Dame Kathleen Lonsdale and June Sutor; their studies were either of smaller collections of stones relating to specific geographical areas or retrospective historical surveys (Lonsdale *et al.*, 1968). They also studied some of Yelloly's calculi and confirmed his analyses.

There was, however,, a chasm between the crystallographic laboratory with its expensive, dedicated equipment and the ordinary hospital laboratory in which stone analysis had not advanced significantly since 1830. In some laboratories an occasional spot test was grudgingly performed, often by the most junior members of staff. Some of these spot tests were more sensitive than others; as a result the presence of phosphates was overreported and that of oxalates masked. The first attempt to apply routine methods of quantitative assay to stones as well as body fluids appears to have been made by Hodgkinson *et al.* (1969) but this was used only for calcium-containing stones. A more comprehensive system was that of Westbury and Omenogor (1970), who added assays of magnesium ammonium and urate to the repertoire. The disadvantage of this approach, however, was that it measured not molecules themselves but only cations and radicals. In this respect it was inferior to crystallography but its great advantage was its cost effectiveness, involving the laboratory in no additional expenditure.

The quest for more accurate and specific means of quantitative analysis continued. Amongst the physical methods tried were the simple technique of relative density comparison and the more sophisticated ones of gamma ray absorption, infrared spectroscopy and polarising microscopy. In our experience the most convenient technique for the small laboratory is the use of the thermogravimetric balance, which has been in use in the author's hospital for 16 years. As we have seen, the principle on which it is based was foreshadowed by the work of Joseph Black in 1751 and this formed an integral part of the research which culminated in the statement of the basic laws of chemistry by Dalton in 1808. For Black and Dalton, the weighing and the heating were two distinct painstaking processes, whereas modern technology allows the plotting of temperature change against weight loss with ease.

The first suggestion that this simple process might be used for stones was made by Strates (1966). In 1969 Strates and Georgacopoulou published thermoanalytic models for the common types of stone and their work was replicated by Berenyi and Liptay in 1971. In 1972 thermogravimetric analysis was used for the first time in the routine analysis of stones from the patient and the results were published by Rose and Woodfine (1976). This technique is used in the author's laboratory in combination with an improved system of the wet chemistry technique described by Westbury and Omenogor (1970).

There remains, however, one final, insoluble problem; most stones are heterogeneous and may have quite different compositions at the centre and in the periphery. Yelloly (1830) approached this problem by dissecting the calculus from the centre outwards; had he possessed the means to quantify his results his reports would have read like geological surveys and would have proved too detailed for clinical purposes. Unfortunately, the geometrical centre of a stone may not be its nucleus; in staghorn calculi it is difficult to detect from the external appearance any kind of centre. "Mulberry' stones do not have a single nucleus; each lobe has a structure of its own and the whole may be embedded in material of a different chemical nature. One possible solution, which has been tried in the author's institution, is to pulverise the entire stone in a machine like a miniature cement mixer; this has now been abandoned on the grounds that it is too slow. In addition, reducing the entire sample to a homogeneous mixture presupposes that the analyst has been given the entire stone; this is often not the case, especially with the advent of shock-wave lithotripsy, and the calculus may be recovered "by instalments".

The overwhelming evidence from analysts over a period of 2 centuries is that the nucleus, if there is one, may differ in composition from the bulk of the stone. Sometimes the nucleus is so minute and so inextricably mixed with other constituents that this difference cannot be proved. One method of tackling this has been to resort to microscopy of one form or another. The first person to use a microscope to examine stones seems to have been a Belfast clergyman, Dr Kirkpatrick (quoted in Hartley, 1739), who looked at stones that he himself had voided after dosing himself with Mrs Stephens' soap solution. His findings, brown particles and a thick white sediment, suggest a mixture of oxalate and phosphate rather than uric acid, so his faith in the soap treatment was misplaced. Today, the leading advocate of stone microscopy is Cifuentes Delatte whose most recent paper appeared in 1987. He believes that the structure of the specimen should be studied carefully with a low-power stereoscopic microscope before any destructive analytical techniques are employed in order to locate, if possible, the elusive nucleus.

It is unwise to use history as a map of the future but it is surely admissible to use the history of science to predict a logical outcome. The ideal tool for stone analysis would be a probe capable of identifying individual molecules in a stone section. Current developments in Fourier Transform Infra-Red technology (FTIR) may herald this exciting achievement. At St Bartholomew's Hospital, Levison *et al.* (1988) developed a method for locating minute traces of oxalate in tissue sections using a combination of FTIR and infra-red microscopy. A minor alteration in the optics of such a system, enabling the use of a reflected rather than a transmitted beam, might allow opaque surfaces rather than transparent sections to be studied. This would mean that one could finally dispense with those mediaeval laboratory relics, the pestle and mortar. The only sampling technique required would be a judicious tap or two to split the stone apart and reveal its interior anatomy. The final consequence of such non-destructive methods of analysis might be that the modern urolithiasis victim could, if he so wished, stick the stone back together with super-glue and, like Samuel Pepys, carry it around as a prophylactic against further calculi for the rest of his life.

Appendix

Stone Constituent Synonyms (Compiled from Dana's System of Mineralogy [1944])

Present chemical name	*Also known as*
Calcium oxalate monohydrate	Oxalate of lime (Wollaston, 1797) Whewellite
Calcium oxalate dihydrate	Weddelite (Prien and Frondel, 1947)
Calcium hydrogen phosphate	Phosphate of lime (Wollaston, 1797) Epiglaubite Brushite
Calcium orthophosphate	Phosphate of lime (Wollaston, 1797) Whitlockite
Calcium phosphate—carbonate complex	Tartar (Bracken, 1739, Hales, 1740) Apatite
Magnesium ammonium phosphate	Phosphate of ammoniaco-magnesia (Wollaston, 1797) Triple phosphate, Struvite
Magnesium hydrogen phosphate	Newberyite
Uric acid	Lithic acid (Scheele, 1776)
Ammonium urate	Lithate of ammonia (Scheele, 1776)
Cystine	Cystic oxide (Wollaston, 1810)

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Risk Factors for Urinary Calcium Oxalate Crystals as Revealed by their Specific Enzymatic Assay

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Summary—Calcium oxalate crystal concentrations were assayed by a new highly specific enzymatic method in 1200 urine samples from normal subjects and stone formers. Examination of the crystals was also carried out by light microscopy and urines were analysed for oxalate, calcium, magnesium, citrate, urate, pH and osmolality.

A striking positive correlation was established between urinary oxalate concentration and calcium oxalate crystal concentration as well as incidence of calcium oxalate crystals and aggregates seen by microscopy. A less striking relationship, also supported by light microscopy, was found between calcium oxalate crystal concentration and urinary calcium concentration. A small rise in calcium oxalate crystalluria was seen with increasing osmolality, but no relationship found between concentration or urinary urate, citrate or magnesium and that of calcium oxalate crystals. Higher levels of calcium oxalate crystal concentration appeared in alkaline urines in association with calcium phosphate.

The dominance of urinary oxalate as a risk factor for calcium oxalate crystalluria is confirmed.

An association between "sand" in urine and the presence of renal stones has been noted from antiquity. Only in the last 2 decades, however, has insight been gained into the origins of crystalluria, if not its relationship to stone growth. Inquiries have extended from simple identification of crystal types to more precise measurements of crystal volumes and sizes under physiological conditions (Robertson, 1969) and the influence of urinary constituents upon crystal formation (Welshman and McGeown, 1972), whilst the formation of urinary crystals has been simulated by continuous crystalliser, reverse osmosis and evaporation techniques (Miller *et al.*, 1977; Hallson and Rose, 1978; Azoury *et al.*, 1986).

Although assay of calcium crystal volume has been possible for many years (Robertson, 1969), the specific determination of urinary calcium oxalate crystal concentrations has eluded investigators until recently (Hallson and Rose, 1988). The present study exploits this specific chemical assay to re-examine calcium oxalate crystalluria and chemical factors influencing the degree of crystalluria in some 1200 random urine samples from normal subjects and stone formers. Urinary calcium oxalate crystals in these samples were also examined by light microscopy and the results of this parallel study are reported herewith.

Methods

A total of 1173 freshly voided urine samples from nearly 600 stone formers attending a metabolic stone clinic and 18 normal volunteers were collected in Dewar flasks and the urinary sediments following centrifugation examined by light microscopy at 37° within 90 min (Hallson and Rose, 1976). Those urines that were crystal-free were evaporated by use of a rotary evaporator (Hallson and Rose, 1978) and the deposits immediately examined by light microscopy. In addition, aliquots from untreated and evaporated urine samples were withdrawn for determination of oxalate and phosphate crystal concentrations by chemical analysis (Hallson and Rose, 1988).

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Untreated urine samples were further analysed for calcium and magnesium by atomic absorption flame spectrophotometry, citrate and urate by enzyme assays with citrate lyase and uricase respectively and for oxalate by the continuous flow procedure of Kasidas and Rose (1985). Urine pH was measured by glass electrode and osmolality with a Wescor 5100c vapour pressure osmometer. Data were accumulated and analysed with the aid of a BBC-B microcomputer and database program.

Results

A characteristic of the results throughout this work was the non-Gaussian and positively skewed frequency distributions of urinary calcium and oxalate crystal concentrations. Thus mean values of crystal concentrations would be unrepresentative. Transformation to the log mode still left positive skews and so median values of the raw data have been used throughout the study.

Figure 1 shows the relationship between the median value of calcium oxalate crystal concentration and corresponding combined urinary oxalate concentrations in normal subjects and stone formers. A slow and gradual increase in crystalluria occurs up to 0.5 mmol/l urine oxalate until a point of inflexion near this upper limit of normal oxalate above which there is a steep rise in precipitated calcium oxalate. This increase is primarily a result of rising urine oxalate and not due to a concomitant rise in urine calcium concentration (Fig. 2). Urine calcium has been restricted to below 4 mmol/l, despite which a similar histogram to Figure 1 appears again with a point of inflexion near the top of the normal urinary oxalate range. Figure 3 shows that under microscopic examination the incidence of envelope oxalate crystals reflects the direct relation found between urine oxalate and calcium oxalate crystal concentration. Figure 4 shows the increases in microscopically observed envelope oxalate aggregated crystals and dumb-bell calcium oxalate monohydrate crystals in relation to urinary oxalate. Whilst both are directly related to urine oxalate, the dumb-bell form occurs infrequently at low oxalate concentrations but rises sharply at concentrations above 0.7 mmol/l. The incidence of aggregated envelope oxalate crystals increases steeply, rising from less than 1% incidence below 0.1 mmol/l urine oxalate concentration to nearly 43% when urine concentration lies between 1.0 and 2.0 mmol/l.

Figure 5 shows the median value of calcium oxalate crystal concentration in relation to urinary calcium levels where urine oxalate concentrations are unrestricted. Whilst this indicates a rise in oxalate crystalluria with urine calcium, the magnitude of the increase is much smaller than that induced by increases in urine oxalate within the observed range (Figs. 1 and 2). The representation in Figure 5 may be attributable in part to an

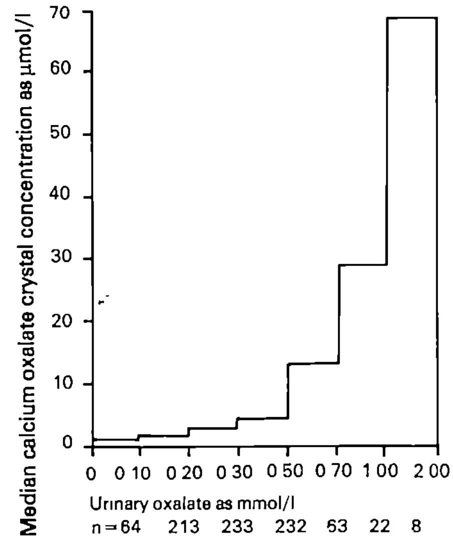

Fig. 1 Urinary oxalate concentration in relation to median calcium oxalate crystal concentration in stone formers and normal individuals

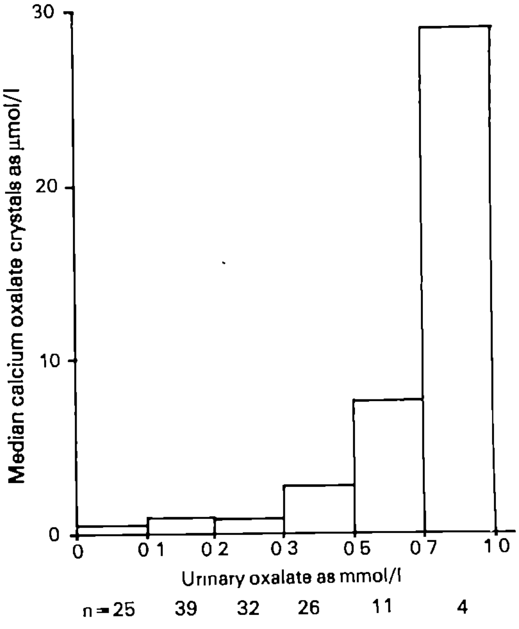

Fig. 2 Urinary oxalate concentration in relation to median calcium oxalate crystal concentration in stone forming subjects Urine calcium is less than 4 mmol/l in all samples included.

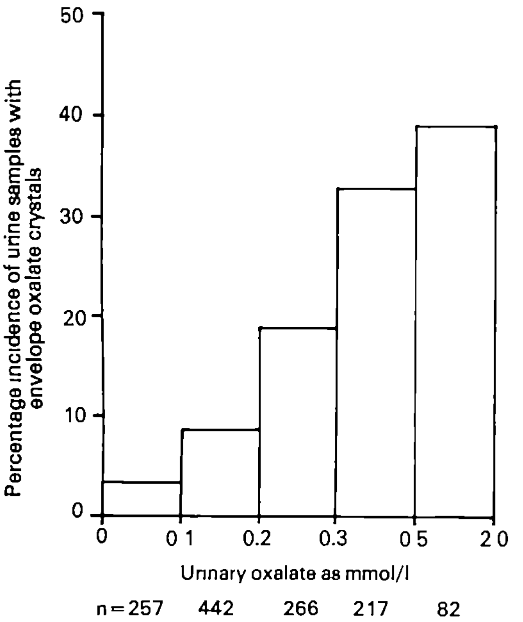

Fig. 3 Urinary oxalate concentration in relation to the frequency with which envelope oxalate crystals are seen by light microscopy in stone forming patients.

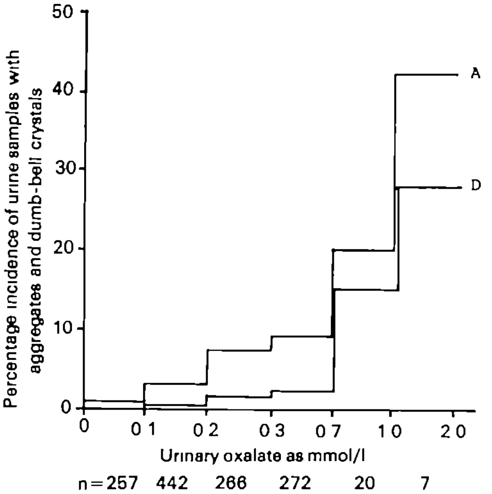

Fig. 4 Frequency with which envelope aggregates and dumb-bell calcium oxalate crystals are seen versus oxalate concentration in stone formers. A and D indicate aggregates and dumb-bells respectively

increase in urinary oxalate correlated with higher calcium concentrations. This effect will be offset when median values of calcium oxalate crystal concentration are examined within a limited urinary oxalate band. Figure 6 shows that despite restriction of urinary oxalate, the direct correlation

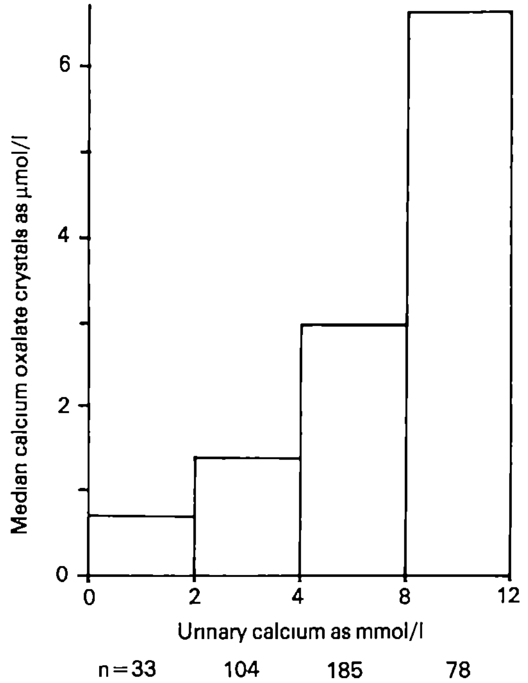

Fig. 5 Urinary calcium concentration in relation to median calcium oxalate crystal concentration where urinary oxalate levels are unrestricted.

between calcium oxalate crystalluria and urine calcium remains.

The results shown in Figure 6 are mirrored by a corresponding increase in the frequency of appearance of envelope oxalate crystals when the urinary oxalate values are restricted within a limited range (Fig. 7).

Overall increases in concentrations of all urine constituents are correlated with increases in osmolality. Changes in calcium oxalate crystal concentration with osmolality are shown in Figure 8. Increases in calcium oxalate crystalluria found are proportional to osmolality, as might be expected, but the magnitude of such increases are small.

Changes with pH of the median urinary calcium oxalate crystal concentration in stone formers are shown in Figure 9. A slight fall in crystalluria occurs with rising pH to 6.0–6.4. Above this pH the amount of calcium oxalate precipitated increases markedly.

Figure 10 shows a correlation between median values of calcium oxalate concentration and the urinary concentration of urate. This figure ignores the effects of rises in urinary calcium and oxalate concentration which accompany increasing urate concentration (Fig. 11). Figure 12 shows that when

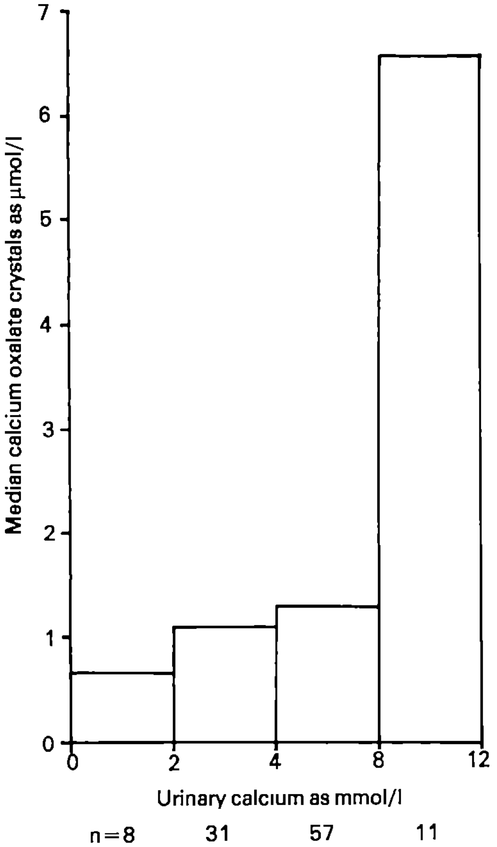

Fig. 6 Relationship between urinary calcium concentration and median calcium oxalate crystal concentration in a limited urinary oxalate concentration range of 0 1–0.2 mmol/l.

urinary calcium is limited to below 8.5 mmol/l, and urinary oxalate restricted to below 0.55 mmol/l no clear correlation appears between calcium oxalate crystalluria and urinary urate concentration.

Discussion

This study is thought to be unique in using the first specific assay of calcium oxalate crystal concentration in urine. Examination of 1200 freshly voided whole urine samples kept at 37° from both normal individuals and stone formers forms the basis of this inquiry.

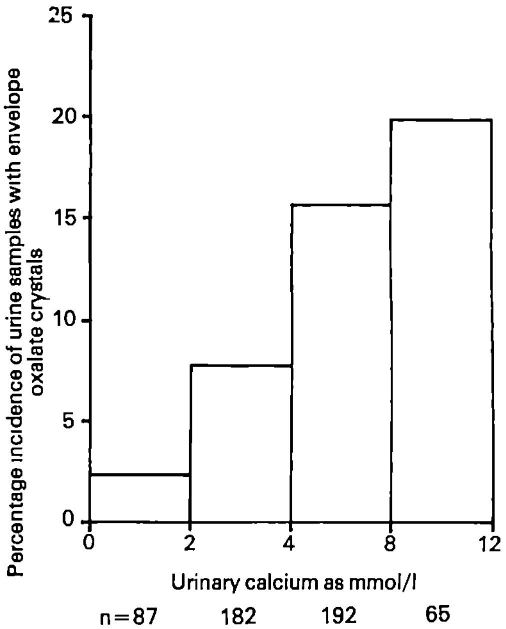

Fig. 7 Percentage incidence of envelope oxalate crystals in relation to urinary calcium in a low and limited urinary oxalate range (0 1–0.3 mmol/l).

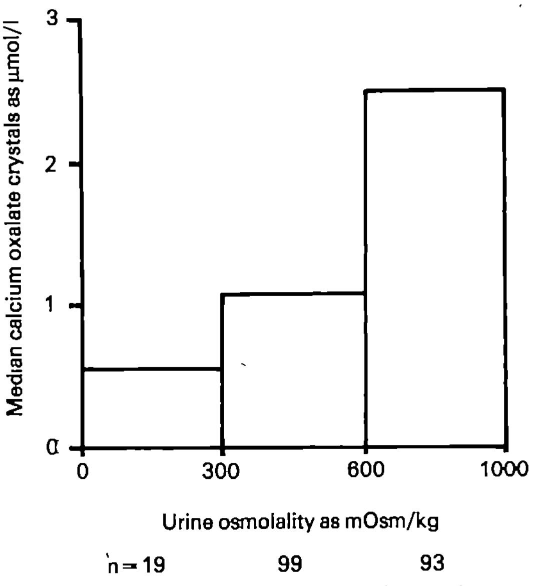

Fig. 8 Urine osmolality in relation to calcium oxalate crystal concentration in stone formers.

Figure 1 shows a striking relationship between calcium oxalate crystal concentration and urinary oxalate concentration. However, before accepting these observations as having a direct cause and effect relationship, one should consider the possibility of a correlation between increasing urinary oxalate concentration and the concentration of many other urinary constituents as shown by Figure 8. Thus urinary calcium oxalate crystal concentration, with rising urinary oxalate, might have been due to a concomitant rise in urinary calcium concentration. This possibility is countered by 3 pieces of evidence. First, the crystal concentration

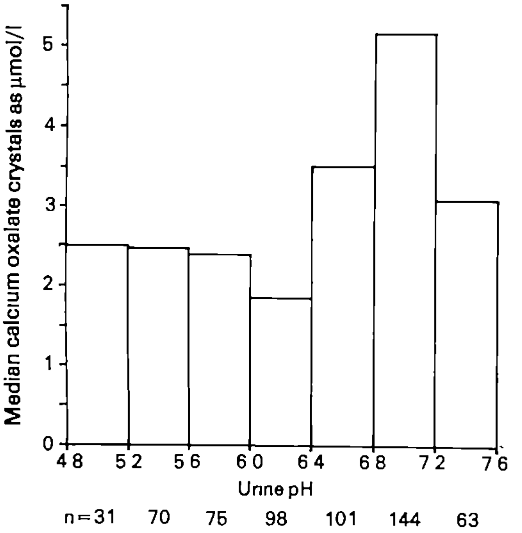

Fig. 9 Urine pH versus median calcium oxalate crystal concentration in stone formers' urine

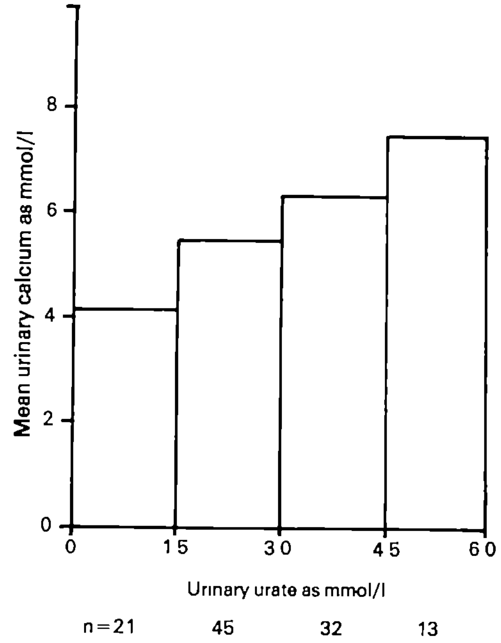

Fig. 11 Correlation between urinary calcium and urinary urate concentrations (mean values)

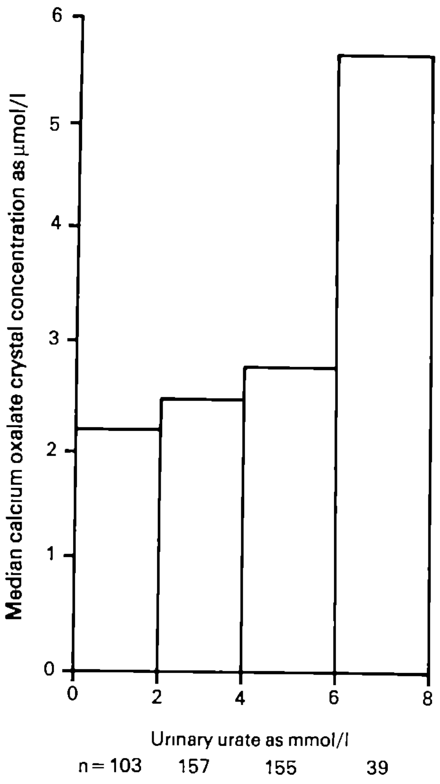

Fig. 10 Urinary urate concentration in relation to median calcium oxalate crystal concentration in stone formers

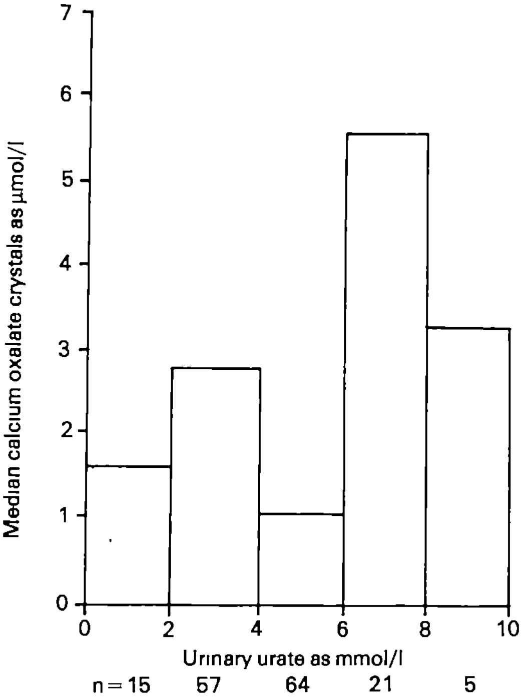

Fig. 12 Urinary urate concentration in relation to median calcium oxalate crystal concentration in stone formers' urine in which urinary oxalate was limited to below 0 55 mmol/l and urinary calcium to below 8 5 mmol/l.

shown in Figure 8 represents only a small fraction of that in Figure 1. Second, in Figure 2 all urine samples with urinary calcium concentration exceeding 4 mmol/l have been excluded, despite which oxalate remains an important factor. Third, overall concentration is restricted in evaporated urine samples since these have been concentrated to a constant osmolality. Within this group no correlation between urinary calcium and oxalate was found, but despite this finding, the same pattern in the relationship of urinary oxalate to calcium oxalate crystal concentration was observed. Precipitation rises gradually to 0.5 mmol/l, until the point of inflexion, above which there is significantly increased calcium oxalate precipitation. These findings agree with earlier theoretical predictions and experimental titrimetric studies (Robertson and Nordin, 1969) and with calcium oxalate crystal concentrations measured by the Coulter particle counter (Robertson *et al.*, 1979). No previous method for determining crystal concentrations has equalled the specificity inherent in the assay used in the present study. Moreover, the numbers of urine samples assayed for crystals far exceeds those in earlier quantitative studies.

It is clear from Figure 1 that increases in urinary oxalate above the normal urinary oxalate range are likely to be far more deleterious than those occurring within the range. The result emphasises the significance of even mild hyperoxaluria in the genesis of calcium oxalate crystals and probably, also, of calcium oxalate stones.

Rising urinary oxalate resulted in a number of other changes in crystals examined. First, the frequency with which envelope oxalate crystals are seen by microscopy increased, as depicted in Figure 3, although here no point of inflexion appears. Second, there was a positive correlation between urinary oxalate and sightings of aggregated envelope oxalate dihydrate crystals and also to "dumb-bell", "hour-glass" and "oval" crystals of calcium oxalate which can be either mono- or di-hydrate (Berg *et al.*, 1976). Both aggregates of envelopes and "dumb-bell" crystals are rarely seen when the urinary oxalate is low but appear in 43 and 30% of urines respectively when the urine oxalate lies between 1 and 2 mmol/l. Dumb-bell crystals may be of metabolic or dietary origin (Catalina and Cifuentes, 1970; Berg *et al.*, 1976) and are themselves polycrystalline agglomerates which may in part account for the similarity in incidence to aggregates of envelope type calcium oxalate dihydrate crystals.

In contrast to the effects of urinary oxalate concentration, previous theoretical and experimental work relating urinary calcium to calcium oxalate crystalluria suggested that only abnormally high levels of urinary calcium were likely to result in increased calcium oxalate precipitation (Robertson and Nordin, 1979). Furthermore, when urinary calcium values from a group of recurrent stone formers were plotted in relation to calcium crystalluria, as measured by Coulter counter, no correlation could be seen (Robertson *et al.*, 1979). These results are not confirmed by the present study. Figure 5 reveals that median calcium oxalate crystal concentrations are directly related to urinary calcium levels. When urinary oxalate is limited to low concentrations within a narrow band (0.1–0.2 mmol/l), as in Figure 6, a pattern similar to Figure 5 emerges. Figure 7 supports these results, showing that the frequency with which envelope oxalate crystals are seen under the microscope is in direct relation to urinary calcium concentration.

Figure 9 shows that minimal calcium oxalate crystal concentration appears between pH 6.0 and 6.4. This concurs broadly with earlier findings relating to changes in calcium crystal volume across the urinary pH spectrum (Robertson *et al.*, 1969). However, the highest concentrations of calcium oxalate were precipitated in more alkaline urines and always in association with calcium phosphate. This is to be reported more fully elsewhere and is not discussed here.

At first sight, Figure 10 suggests a direct proportionality between calcium oxalate crystal concentration and urinary urate, but this neglects an evident positive correlation between urinary calcium and urinary urate (Fig. 11). When urine calcium is limited to less than 8.5 mmol/l, and urine oxalate to below 0.55 mmol/l, as in Figure 12, no association between crystalluria and urate concentration is apparent. The median value of calcium oxalate crystal concentration for all samples in Figure 11 was 2.71 μmol/l. When the samples were divided into those containing less than or more than 5 mmol/l urate, 52 of the former exceeded the overall median calcium oxalate crystal concentration whilst 54 were below the median. Of urines with more than 5 mmol/l urate, 29 exceeded the median and 27 did not (Chi-square=0.0273, $P=0.87$, n.s.). These results, therefore, do not provide support for the suggestion that lowering urinary urate diminishes calcium oxalate crystalluria (Kallistratos *et al.*, 1970; Robertson *et al.*, 1976; Coe, 1980) but supports previous direct evidence that urate does not increase calcium oxalate crystalluria (Hallson *et al.*, 1982a).

It is hard to dispute the evidence that magnesium and citrate ions diminish calcium oxalate crystallisation in urine (Elliot *et al.*, 1956; Lyons *et al.*, 1966; Dent *et al.*, 1970; Sutor *et al.*, 1979; Hallson *et al.*, 1982b, 1983). However, in the present study no clear relationship was discernible when calcium oxalate crystal concentrations were plotted against urinary magnesium or citrate levels (as scatter graphs). This unexpected outcome may derive from samples examined. Unlike *in vitro* inhibitor tests, no control was possible over urinary solutes, macromolecules, colloids and particles in random urines. It is likely that these constituents, together with the wide variations in crystal concentrations observed (between 0.1 and 500 μmol/l) may have been sufficient to mask the crystal inhibitory effects of both magnesium and citrate within their physiological concentration ranges. Such results do not imply that these substances are ineffective inhibitors. For while this may be so within the normal concentration ranges of this study, it may still be true that inhibitor effects of citrate and magnesium may be observable over wider concentration ranges.

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Measurement of Calcium Phosphate Crystalluria: Influence of pH and Osmolality and Invariable Presence of Oxalate

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Summary—Calcium phosphate and calcium oxalate urinary crystal concentrations in normal and stone-forming subjects were measured. The urinary crystals were examined by light microscopy and urine samples were analysed for oxalate, pH and osmolality.

Calcium phosphate crystal concentrations were clearly related to urine pH but unrelated to urine osmolality. An unexpected finding was co-precipitation of oxalate with calcium phosphate. Consequently, precipitated invariable oxalate increased with rising urinary pH. Possible explanations and implications are discussed.

Calcium phosphate is the second most prevalent constituent of upper urinary tract stones found in industrialised countries. Acidic, neutral and basic forms of calcium phosphate have been reported as crystalline constituents of urinary calculi (Sutor, 1976). In treated and untreated stone formers and normal individuals, calcium phosphate is the most frequent crystal type observed by light microscopy as determined in the present study and also in an earlier one (Hallson and Rose, 1976). Whilst the occurrence of recognisable forms of calcium oxalate with calcium phosphate has been reported by the presented authors and others (Robertson *et al.*, 1969), the possibility that calcium oxalate may be regularly present along with mainly calcium phosphate in a form which could not be identified by light microscopy does not seem to have been previously considered. The present study provides evidence for this and also for urinary pH as being the principal determinant of calcium phosphate crystal concentrations.

Materials and Methods

This study formed part of a larger microscope and quantitative chemical investigation of crystalluria in 1173 freshly voided urine samples from nearly 600 stone formers and 18 normal subjects (Hallson and Rose, 1988). The samples were collected in Dewar vessels and urinary sediments from these were examined by light microscopy at 37° within 90 min, following centrifugation in a warm room. Crystal-free urines were evaporated at 37° to 1200 mOsm/kg/ ±25 mOsm/kg by means of a rotary evaporator (Hallson and Rose, 1978) prior to immediate examination by light microscopy. Aliquots from untreated urines were withdrawn for determination of oxalate and phosphate crystal concentrations (Hallson and Rose, 1988). Calcium phosphate crystal concentrations were derived from assay of phosphate alone. The molar concentration of calcium ions may differ according to the composition of the calcium phosphate precipitate. Accordingly, where appropriate in the Figures, the word calcium may appear in brackets. Untreated urine samples were analysed for calcium by atomic absorption flame spectrophotometry and for oxalate by the continuous flow method of Kasidas and Rose (1985). Urine pH was measured by glass electrode and osmolality determined using a Wescor 5100 C vapour pressure osmometer. Data accruing were saved and analysed with the aid of a BBC microcomputer and database program.

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Results

Calcium phosphate was the most frequently observed precipitate, appearing in almost 22% of the urine of stone formers and 16% of the urine of normal individuals as determined by microscopy. Figure 1 shows the percentage of urine containing envelope-type calcium oxalate dihydrate crystals and calcium phosphate (mainly in amorphous or stellar form) across the urine pH range as observed under light microscopy. Calcium phosphate crystals increase in incidence with rising urine pH, whilst the opposite seems true for calcium oxalate.

Where urine deposits consisted mainly of amorphous or stellar calcium phosphate, calcium oxalate crystals in their identifiable envelope or dumbbell habit were infrequently seen. Furthermore, when such sightings were made, calcium oxalate crystals were always very few in number when compared with those seen in more acidic urines.

Figure 2 supports microscope observations showing increasing calcium phosphate crystal concentrations in untreated and evaporated urines with rising pH. On the other hand, no clear relationship could be found between calcium phosphate crystal concentrations and the osmolality of the urine in which the crystals formed.

Figure 3 shows calcium phosphate crystal concentrations in relation to those of calcium oxalate found in precipitates which appeared under the microscope to be entirely amorphous calcium phosphate. This indicates the presence of oxalate in an amorphous or crystalline form not discerned by light microscopy. This scatter graph, which was derived from both untreated and evaporated urine samples from stone formers, shows a discernible positive correlation between calcium phosphate and calcium oxalate (r = 0.51) (Table).

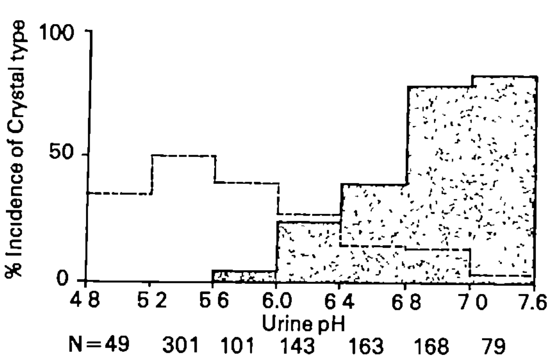

Fig. 1 Effect of urinary pH on incidence of crystal types observed by light microscopy The proportion of urine samples containing envelope-type calcium oxalate crystals (broken line) decreases with rising pH, whilst the reverse is true for calcium phosphate crystalluria (solid line; stippled zone) N = No of samples in each pH range.

The proportionality of calcium phosphate to calcium oxalate is further evident in Figures 4 and

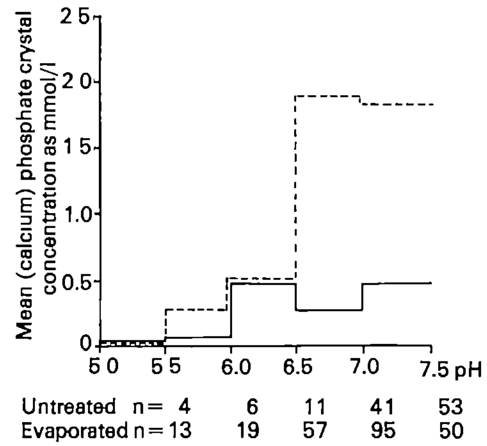

Fig. 2 Effect of urinary pH upon mean calcium phosphate crystal concentration. Crystal concentration rises with pH, as expected from Figure 1. The broken and solid lines represent evaporated and untreated urine samples respectively N = No of samples in each pH range.

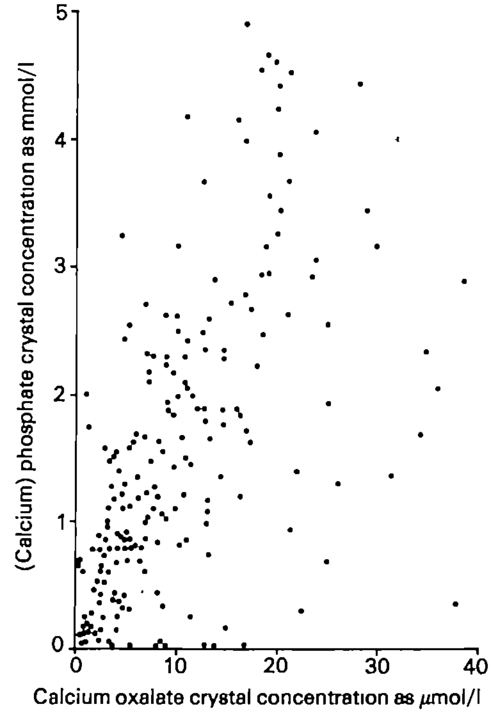

Fig. 3 Correlation between calcium phosphate and calcium oxalate crystal concentrations found in 198 untreated and evaporated urine samples plotted as a scatter graph. Of the 331 possible points it was necessary to omit 133 where calcium phosphate concentration was below 0 6 mmol/l in order to avoid overcrowding Statistics from this chart are shown in the Table.

Table Statistical Data from Figure 3 (including points not shown)

	Intercept	*Slope*	*R*	*t*	*P*	df	*Calcium phosphate / Calcium oxalate*
Estimating y from x							
All data	0.38	0.10	0.631	14.77	<0.001	329	180
Unevaporated urine	0.81	0.08	0.558	3.92	<0.001	34	320
Evaporated urine	1.23	0.08	0.503	6.5	<0.001	125	230
Estimating x from y							
All data	3.09	4.17	As above				
Unevaporated urine	1.41	3.74					
Evaporated urine	6.65	3.22					

5. In drawing these figures, data were derived from urine where the phosphate crystal concentrations exceeded 0.6 mmol/l to enable more accurate ratios of calcium phosphate to calcium oxalate to be obtained. Figure 5 shows the frequency with which molar ratios of calcium phosphate to calcium oxalate were observed in precipitates from untreated urine. The mean ratio was 284:1. The corresponding ratio for precipitates formed by evaporation of crystal-free urine was 191:1 (Fig. 4).

Figure 6 shows that relatively high concentrations of calcium oxalate crystals (chosen as those greater than 5 μmol/l) are more frequent in alkaline urines. In keeping with the foregoing results, calcium oxalate precipitation appearing in alkaline urine has occurred in association with calcium phosphate.

Whilst no correspondence was found between crystal concentration ratios and the pH of the urine in which the precipitates formed, Figure 7 shows a clear negative relationship between mean ratios of precipitated calcium phosphate to calcium oxalate as the concentration of oxalate in the urine rises.

Discussion

In both untreated and evaporated urine, rising pH leads to increased calcium phosphate crystal concentration (Fig. 2). This concurs with the earlier work of Robertson *et al.* (1969), who also observed the occasional appearance of calcium oxalate in urine above pH 6.2 where deposits consisted mainly of amorphous calcium phosphate. This agrees with the microscope findings in the present study (Fig. 1) and with our earlier results (Hallson and Rose,

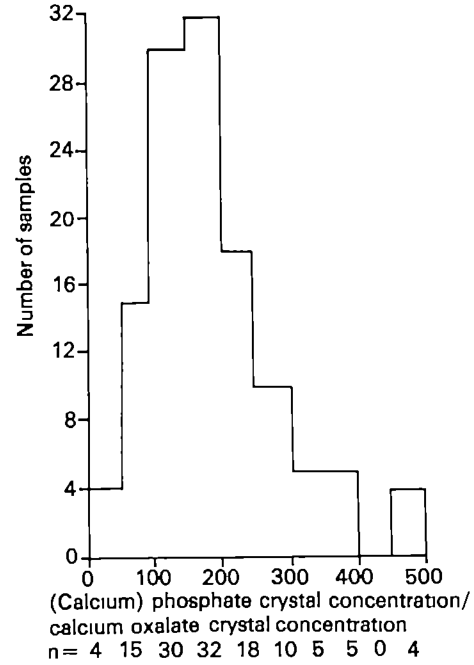

Fig. 4 Incidence of calcium phosphate to calcium oxalate crystal concentration ratios in evaporated urine.

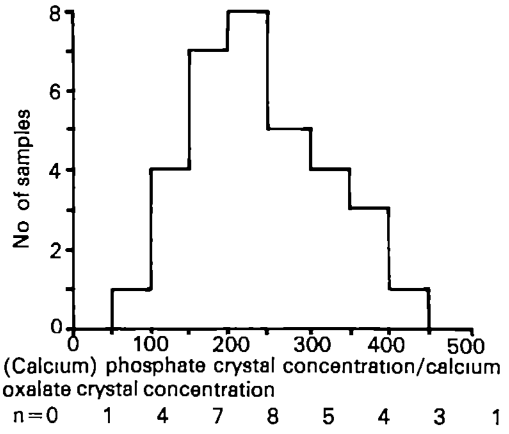

Fig. 5 Incidence of calcium phosphate to calcium oxalate crystal concentration ratios in untreated urine

1976). In the meantime, tacit acceptance seems to have been accorded to the belief that calcium oxalate crystallises mainly from more acid urine and calcium phosphate from more alkaline urine.

Urine osmolality was, unexpectedly, found to have no clear relationship to calcium phosphate crystal concentrations. This may be due in part to the abrupt manner in which calcium phosphate sometimes precipitates from otherwise crystal-free urine.

Enzymatic determination of calcium oxalate crystal concentrations applied to urine containing calcium phosphate precipitates yielded 2 surprising results. Firstly, from Figure 3 it may be seen that oxalate, ostensibly as calcium oxalate, is present with all observed calcium phosphate precipitates, often in higher crystal concentrations than in more acid urine (Fig. 6). Secondly, there is a discernible correlation between the concentrations of the 2 crystal compounds. The frequency distribution ratio of calcium phosphate crystal concentrations to those of calcium oxalate found in untreated urine is shown in Figure 5 and gives a mean molar ratio of calcium phosphate to calcium oxalate of 284:1. The corresponding mean molar ratio for evaporated urine is 191:1 (Fig. 4). Although this difference is not significant, a possible reason is discussed later. In Figures 4 and 5, urine samples were selected to have calcium phosphate concentrations above 0.6 mmol/l. This ensured that the precipitates were predominantly those of calcium phosphate and also ensured the good analytical accuracy required to calculate the molar ratios.

There are a number of possible forms in which oxalate may be associated with calcium phosphate precipitates. The large excess of calcium phosphate does not rule out the presence of a calcium-oxalate-phosphate complex salt in small volume. Alternatively, an amorphous form of calcium oxalate or one in which the familiar envelope habit of these crystals is too small to be resolved by light microscopy may occur. Hydroxyapatite present in amorphous calcium phosphate is a known adsorbant and may bind oxalic acid. However, a more plausible hypothesis is epitaxial growth of calcium oxalate upon the hydroxyapatite, since this is supported by experimental evidence (Londsdale, 1968; Meyer *et al.*, 1975). Seed crystals of hydroxyapatite have been shown to induce the growth of calcium oxalate monohydrate crystals epitaxially from a metastable supersaturated solution of calcium oxalate. The relatively high proportions of oxalate present in post-evaporation calcium phosphate precipitates may arise from the large surface area offered by the newly formed small calcium phosphate crystals which rapidly relieves calcium oxalate supersaturation. This would not be so with calcium phosphate crystals isolated from untreated urine, where a long bladder residence time might allow further growth of crystals with calcium phosphate. Meyer *et al.* (1975) confirmed that the rate of epitaxial growth of calcium oxalate upon hydroxyapatite was proportional to the surface area of the latter.

Increasing urine oxalate concentrations give rise to a precipitate which is richer in oxalate (Fig. 7). This almost certainly reflects the higher supersaturation with respect to calcium and oxalate and the

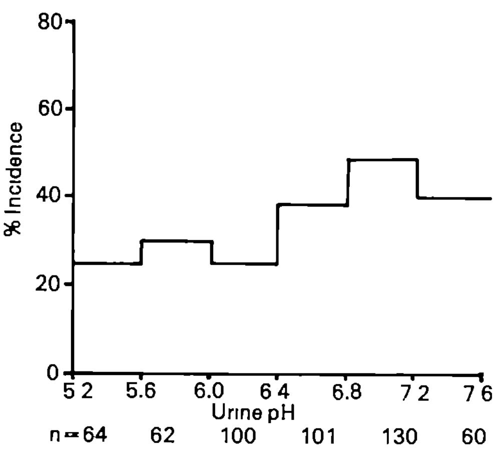

Fig. 6 Percentage incidence of calcium oxalate crystal concentrations above 5 μmol/l in relation to pH in the urine of stone formers.

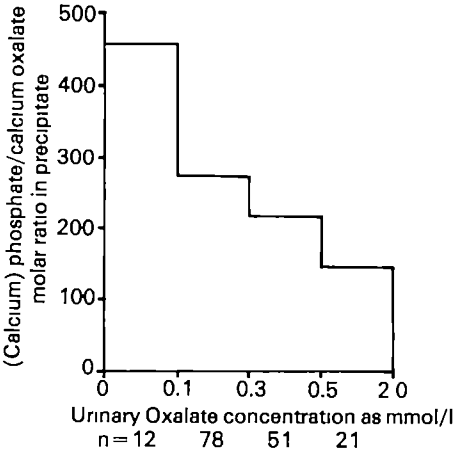

Fig. 7 Effect of increasing urinary oxalate concentration upon the ratio of calcium phosphate co-precipitated with calcium oxalate in evaporated urine.

consequent tendency to precipitate or to grow upon existing nuclei.

The findings outlined above raise a number of questions. In particular, to what extent does the increasing calcium phosphate precipitation with rising pH constitute a risk factor for calcium phosphate lithiasis (Robertson *et al.*, 1981)? On the other hand, does calcium oxalate co-precipitated in this manner harmlessly relieve urinary concentration of both oxalate and calcium and may this be of benefit to those who are primarily calcium oxalate stone formers? Could this explain how phosphate therapy is effective for calcium oxalate stones (Ettinger and Kolb, 1973)?

Despite the higher levels of calcium oxalate precipitation in alkaline urines, the proportion of calcium oxalate in renal stones formed under alkaline conditions is low. In 15 of 17 kidney stones analysed chemically at St Peter's Group Hospitals from patients with renal tubular acidosis, and in whom the urine pH is unlikely ever to have been low, no calcium oxalate could be detected. The explanation is presumably that the methods of stone analysis are unable to detect calcium oxalate when present only as 1 part in some 200 parts of calcium phosphate.

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Possible Role of Tamm-Horsfall Glycoprotein in Calcium Oxalate Crystallisation

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Summary—The role of Tamm-Horsfall glycoprotein (THGP) in the crystallisation of calcium oxalate was investigated. The results showed THGP to have a weak inhibitory effect on crystal growth. In contrast, urinary macromolecules showed a strong inhibitory effect. THGP should, therefore, not be considered the main component of urinary macromolecules which have a strong inhibitory effect on crystal growth. However, THGP did enhance crystal production in the early phase of crystallisation. It appears that THGP should be viewed as a promoter rather than an inhibitor of calcium oxalate crystallisation at physiological concentrations.

Tamm-Horsfall glycoprotein is one of the major glycoproteins in human urine, but its effect on crystallisation has remained somewhat controversial. Scurr and Robertson (1986a, b) showed that THGP had an inhibitory effect on crystal growth and suggested it could be a potential promoter of crystal aggregation. Kitamura and Pak (1982) noted that THGP exerted a slight inhibitory effect on calcium oxalate crystal precipitation and crystal growth. On the other hand, Rose and Sulaiman (1982) showed THGP to promote calcium oxalate crystal precipitation, while Sophasan *et al.* (1980) showed no influence of THGP on crystal mass formation. Finally, Drach *et al.* (1980) revealed the dual potential of THGP for calcium oxalate crystallisation, an inhibitory effect on crystal growth, as well as an enhancing effect on crystal nucleation.

In this study we have attempted to clarify the possible role of THGP in calcium oxalate crystallisation.

Materials and Methods

Purification of Tamm-Horsfall glycoprotein

Twelve-hour urine samples were collected, without any preservatives, from 11 normal adult males. THGP was purified through a modification of the original method of Tamm and Horsfall (1950) described briefly as follows. NaCl was added to each urine sample to achieve a final concentration of 0.58M. The samples were left to stand for 24 h at 4°C and then centrifuged at 3000 rpm for 10 min at 4°C. The supernatants were discarded and the precipitates washed with 300 ml of 0.58 M NaCl stored at 4°C. After 3 washes, the precipitates were dissolved in 100 ml of distilled water and dialysed against 3 l of distilled water for 24 h at 4°C; 200 ml of cold distilled water were then added to the dialysates, followd by 300 ml of cold 1.16 M NaCl. These steps were repeated twice and the dialysates obtained the third time were centrifuged at 8000 rpm for 15 min at 4°C; the supernatants were then freeze-dried, weighed to calculate urine concentration and stored at −20°C until use.

Urine ultrafiltration

Other 12-h urine samples from the same 11 normal adult males were pooled and 0.02% sodium azide was added as a preservative. This urine was filtered through 0.22μ Millipore filter and pH was adjusted to 5.7 in order to prevent spontaneous crystallisation of calcium phosphate. Ultrafiltration was performed with a molecular weight cut-off of 13,000 daltons; the ultrafiltrate was used in the non-seed crystallisation system. Moreover, the urinary macromolecular fractions were dialysed against distilled water to remove low molecular weight

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material and used in the seed crystal system. These fractions were stored at −80°C until use.

Seed crystal experiment

The effect of THGP on calcium oxalate crystal growth was determined with the seed crystal system according to the modified method of Robertson *et al.* (1973). Metastable synthetic urine was composed of 1 mM calcium chloride, 0.2 mM sodium oxalate, 150 mM sodium chloride and10 mM sodium cacodylate buffer with a trace dose of ^{14}C-oxalate adjusted to pH 6.0. Seed crystals were prepared by adding 100 mg of commercial calcium oxalate monohydrate crystals to 100 ml of distilled water and stirred with a magnetic stirrer. The stored THGP was dissolved in distilled water and 1 ml of the THGP solution added to 10 ml of the synthetic urine to achieve the final THGP concentration of 1 to 100 mg/1; 0.25 ml of the seed crystals was added and the mixture incubated for 4 h at 37°C in a shaking water bath. An aliquot of the mixture was filtered through a 0.22μ Millipore filter, the radioactivity of the filtrate was counted with a scintillation counter, and the amount of oxalate consumed for crystal growth was calculated. The inhibitory activity of the urinary macromolecules was determined in the same manner.

Non-seed crystal experiment

Spontaneous crystallisation was induced by adding sodium oxalate to the synthetic urine or the ultrafiltrate mentioned before; 2 ml aliquots of the sample solution, containing various amounts of THGP, were added to 20 ml aliquots of the synthetic urine or the ultrafiltrate to achieve a final THGP concentration of 1 to 100 mg/1. The addition of 50 mM ^{14}C-labelled sodium oxalate resulted in a 0.5 mM increase in oxalate concentration for the synthetic urine and 1 mM for the ultrafiltrate. The latter value was determined after establishment of the metastable limit of the ultrafiltrate according to the modified method of Ryall *et al.* (1985). The amounts of precipitated calcium oxalate crystals were calculated from the count of radioactivity at the start and at random intervals. These experiments were performed in triplicate at room temperature with shaking.

The inhibition index (I.I.) or the promotion index (P.I.) was determined as follows:

$$\text{I.I.} = Cc - Cs/CcX100\ (\%)$$
$$\text{P.I.} = Cs - Cc/CcX100\ (\%)$$

Cc: amount of control, dpm
Cs: amount of sample, dpm

Results

THGP concentration

THGP concentrations obtained from the 11 normal subjects ranged from 8.3 to 35.7 mg/l (Table 1). These values were used as the basic physiological concentration for the experiments that followed.

Effect of THGP on crystal growth

THGP revealed minimal inhibitory activity, with an I.I. of 2 to 3% at the physiological concentration, on calcium oxalate crystal growth. However, the inhibitory activity showed a tendency to increase with an increment in THGP concentration. On the other hand, the urinary macromolecules revealed strong inhibitory activity even when the concentration was one-tenth that of the original urine (Table 2). This suggests that THGP is not the main component in urinary macromolecules which have a strong inhibitory effect on calcium oxalate crystal growth.

Effect of THGP on spontaneous crystallisation

THGP was found to enhance spontaneous crystallisation in non-seed experiments using both syn-

Table 1 THGP Concentrations of Normal Urine Samples

	No										
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*
THGP (mg/l)	10.9	12.3	8.3	26.9	26.6	35.7	27.1	12.5	29.1	34.9	32.0

Table 2 Calcium Oxalate Crystal Growth Inhibition Index (Seed Crystal System)

	THGP (mg/l)				*UMM (%)*		
	1	*10*	*50*	*100*	*10*	*50*	*100*
I.I (%)	1.8	2.7	2.8	6.9	63.7	80.7	86.7

UMM: urinary macromolecules (M W. > 13,000)

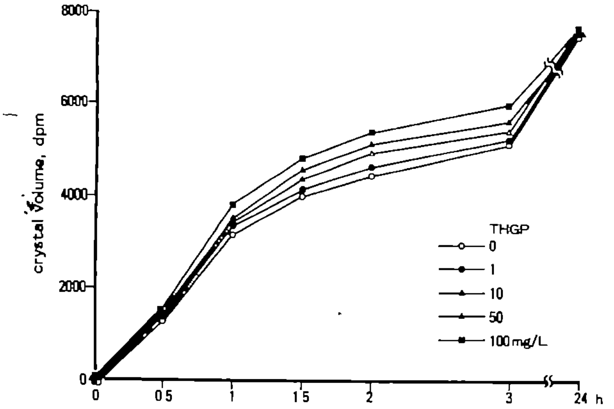

Fig. 1 Time course of crystal volume in a non-seed experiment using synthetic urine

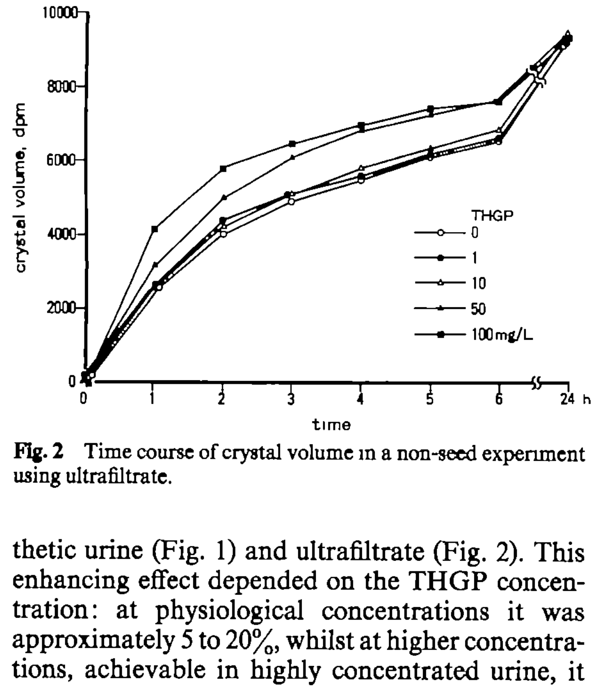

Fig. 2 Time course of crystal volume in a non-seed experiment using ultrafiltrate.

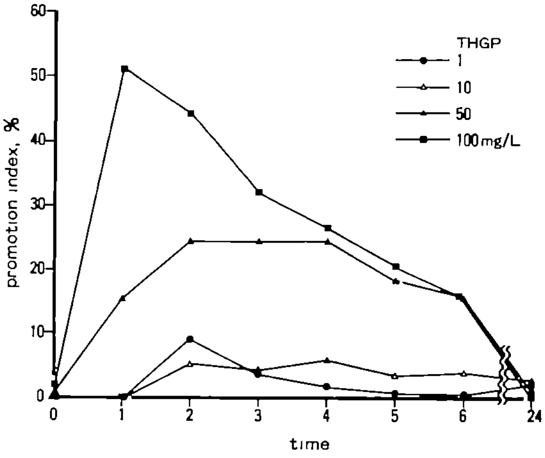

Fig. 3 Promotion index in a non-seed experiment using ultrafiltrate. Note the maximal values are achieved within 2 h of incubation.

thetic urine (Fig. 1) and ultrafiltrate (Fig. 2). This enhancing effect depended on the THGP concentration: at physiological concentrations it was approximately 5 to 20%, whilst at higher concentrations, achievable in highly concentrated urine, it rose to a P.I. of about 50% in ultrafiltrate (Fig. 3). Moreover, this effect was conspicuous at times of incubation less than 2 h, suggesting enhancement of crystal nucleation rather than growth in these experiments.

Discussion

The most widely accepted theory holds that there are several phases in the formation of urinary stones. Spontaneous nucleation is the first step in stone formation and can be induced with homogeneous or heterogeneous mechanisms, either separate or combined. Crystal growth continues until the product of the stone forming salts decreases to the saturation point. Concretion concludes the stone forming process.

It has been established that many substances affect calcium oxalate crystallisation at any stone forming phase. However, the effect of THGP on calcium oxalate crystallisation has remained controversial, with several reports describing THGP as either an inhibitor, a promoter or neither of these. In this study, we have established that THGP affects the nucleation phase as a promoter and the crystal growth phase as a weak inhibitor.

Concerning the effect of THGP on nucleation, Rose and Sulaiman (1982) noted that removal of THGP by means of a rapid rotary evaporation system from the whole urine reduced calcium oxalate deposition; the addition of THGP to the ultrafiltrate lessened this reduction but did not restore the deposition to its original value. They speculated that THGP was a promoter of the nucleation phase by inducing heterogenous crystallisation. Moreover, they noted that the addition of sodium dodecyl sulphate reduced the calcium oxalate precipitation to 64.3 to 53% of the original value and the conversion of uromucoid from the polymeric to the monomeric form reduced the effect of uromucoid as a promoter of crystal formation (Rose and Slaiman, 1984). Their report shows that the action of THGP on crystal nucleation depends on the form in which it exists in the experimental medium and is related to ionic strength, THGP concentration and pH as described by Scurr and Robertson (1986b). They found the promotional activity in relatively concentrated urine. We also recognised the promotional activity in both ultrafiltrate and artificial urine, but the former was considered to have medium ionic strength and the latter relatively low ionic strength. Kitamura and Pak (1982) reported that THGP increased the formation product ratio of calcium oxalate and concluded that THGP did not enhance calcium oxalate nucleation. However, if heterogeneous nucleation were the true mechanism of the nucleation promoting activity of THGP as described by Rose and Sulaiman (1982), the elevation of the formation product ratio would not be important because heterogenous nucleation can be induced in metastably saturated urine. Thus Kitamura and Pak's detection of the elevated formation product ratio cannot lead to the conclusion that THGP does not enhance calcium oxalate nucleation. Sophasan *et al.* (1980) also concluded that THGP did not affect calcium oxalate crystal formation. In their experiments, however, the crystal volume was determined after incubation for 24 h. The present investigation shows that the promotional effect of THGP on crystal volume should be determined after only a few hours of incubation because it is based on nucleation enhancement. We also found no difference in total yielded crystal mass after 24 hours' incubation. By using a continuous crystalliser, Drach *et al.* (1980) recognised uromucoid as a growth inhibitor and nucleation promoter, but they determined the promotional effect by counting the increase in the number of crystals. We consider that an increment in the number of crystals does not necessarily show the promotional effect accurately, because a growth inhibitor can cause the number of crystals, since they are small, to increase without any increment in crystal volume (Edyvane *et al.*, 1987b). The cause of the controversy about the role of THGP seems mainly due to different assay systems producing different results. It is also important to consider the form in which THGP exists in the experimental medium, because the effect of THGP seems to change with ionic strength depending on whether it is in the polymeric or the monomeric form. Further investigations are necessary in order to dissolve the actual effect of THGP *in vivo*.

On the other hand, several authors have recognised the inhibitory effect of THGP on crystal growth (Drach *et al.*, 1980; Kitamura and Pak, 1982; Fellström *et al.*, 1986; Scurr and Robertson, 1986; Edyvane *et al.* 1987a). We also found this inhibitory activity, but it was minimal (less than 5% of the inhibition at physiological concentration). Moreover, urinary macromolecular substances larger than 13,000 daltons derived from healthy pooled urine had a strong inhibitory effect on crystal growth, more than 80% of inhibition at physiological concentration. It is therefore considered that THGP plays a minimal part among urinary macromolecular inhibitors.

THGP excretion was measured only in normal subjects in this study. Boyce and Swanson (1955) and Dulce (1958) found increased uromucoid excretion in stone formers. Bichler *et al.* (1976) recognised the relevance of an increase in uromucoid excretion in calcium-containing stone formers, whereas no increment was found in stone formers of other compositions. These clinical results might support the promotional effect of THGP on calculogenesis in calcium-containing urolithiasis.

In conclusion, THGP probably has a dual effect on calcium oxalate crystallisation, being both an inhibitor of crystal growth and a promoter of nucleation. We believe that at physiological concentrations the inhibitory activity of THGP is so weak that the promotional activity is predominant.

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Recombinant Interferon-alpha with or without Vinblastine in Metastatic Renal Carcinoma

Results of a Randomised Phase II Study

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Summary—In a randomised phase II study, 5 of 24 patients with metastatic renal carcinoma responded to treatment with interferon (IFN) (Roferon A, Roche, Basle, Switzerland) (18×10^6 u i.m. 3 times/week). The combination of IFN with vinblastine (0.1 mg/kg every third week) yielded a response rate of 16% (4 of 25 patients). Three patients continue to show a response (2 complete, 1 partial) more than 20 months after cessation of treatment.

Flu-like symptoms represented the major side effect and often led to modification or discontinuation of treatment.

It was concluded that IFN is the treatment of choice in patients with metastatic renal carcinoma who are candidates for medical treatment. The significance of additional vinblastine is uncertain.

The response rates to cytostatic treatment in metastatic renal carcinoma have been disappointing. In earlier studies, vinblastine (VBL) led to an objective response in 20 to 25% of patients (Hrushesky and Murphy, 1977), but these observations have not been confirmed in newer trials (Tannock and Evans, 1985; Crivellari *et al.*, 1987). In more recent investigations, interferon-alpha has yielded a response rate of about 15% in metastatic renal carcinoma (Quesada *et al.*, 1985; Krown, 1987; Muss *et al.*, 1987; Sarna *et al.*, 1987; Trump *et al.*, 1987). The combination of IFN and VBL has produced even better results (30–40% response rates) (Fosså *et al.*, 1986; Bergerat *et al.*, 1988).

From 1986 to 1987, a European multicentre independent trial (MIT), organised by Hoffmann, La Roche (Basle, Switzerland), was designed to compare the response and survival rates in patients with metastatic renal carcinoma treated with either IFN-alpha (Roferon A) or IFN+VBL. Patients were grouped according to the participating institution. The results of this trial have not yet been published.

The present study deals with observations made during this trial at The Norwegian Radium Hospital. The single-institution study was extended throughout 1987, after closure of the European MIT.

Patients and Methods

The series included 56 patients who were randomised to receive either IFN 18×10^6 u 3 times/week i.m. (treatment A) or IFN+VBL (0.1 mg/kg i.v. every third week) (treatment B).

Criteria for inclusion in the study were: progressive measurable metastatic disease, age ≤ 70 years (≤ 75 years for patients entered in 1987); performance status ≥ 70 (Karnofsky scale); nephrectomy performed at least 4 weeks prior to inclusion; no previous chemotherapy or hormonal therapy. Evaluable patients were to be treated for at least 2 months unless progressive disease developed within that period (early progression) (Table 1).

All patients underwent follow-up examinations at 4-weekly intervals. Evaluation of response and toxicity grading were performed according to WHO recommendations (Miller *et al.*, 1981). The duration

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Table 1 Details of Patients

	IFN	*IFN+VBL*	*Total*
Entered	28	28	56
Ineligible	1	1	2
Eligible	27	27	54
Age (years)	60*	61	61
Males/females	18/9	22/5	40/14
Performance status (Karnofsky)			
90/100	13	16	29
70/80	14	11	25
Nephrectomy before entry to trial	12*	8	9
(months)	(1–110)†	(1–185)	(1–185)
Duration of treatment	107*	102	102
(days)	(7–343)†	(5–317)	(5–343)
Site of indicator lesion			
Lung	18	21	39
Lymph node	5	3	8
Soft tissue	2	2	4
Liver	2	1	3
Not evaluable for response	3	2	5

*Median †Range.

of response was calculated from the start of treatment.

Statistics

The program package "Medlog" was used to calculate medians, ranges and to evaluate differences (Student's t-test, chi-squared test). The 2-year crude survival rate was assessed by the Kaplan Meier method and the log rank test. A P value <0.05 was regarded as statistically significant.

Results

Two patients were deemed ineligible retrospectively (brain metastasis in 1 and no progressive disease prior to trial in the other). Five patients were not evaluable for response (intercurrent death not due to renal carcinoma or treatment toxicity in 1 and <2 months' treatment in 4); 49 patients were evaluable (treatment A: 24 patients; treatment B: 25). Pre-treatment characteristics of patients and details of treatment were evenly distributed within the 2 groups.

Response

Five of 24 patients on IFN alone (response rate 21%, 95% confidence interval: 7–42%) and 4 of 25 on IFN+VBL responded (response rate 16%; 95% confidence interval: 5–36%) (Table 2). Seven of the responses were observed in 39 patients with lung metastases; 2 of 8 patients with measurable lymph node metastases responded partially; 2 complete remissions lasted for 26+ and 29+ months after discontinuation of treatment. In a third patient (treatment A) with initial multiple lung metastases, a 1-cm residual mass remained unchanged 20+ months after discontinuation of IFN.

After 2 months' treatment the median reduction in tumour size was 47% in patients who finally developed an objective response and only 5% in non-responding patients.

Table 2 Response

	IFN	*IFN+VBL*	*Total*
Complete response	1*	1*	2
Partial response	4+	3+	7
No change	15	14	29
Progression	4	7	11
Total	24	25	49
Duration of reponse (months)	*29+	*33+	
	25+	14	
	12	7	
	10	4	
	8		

*Complete response

Survival

No difference in survival was observed for the 2 treatment arms (Fig. 1). There was a significant difference in survival between patients with no change and those with progression (Fig. 2).

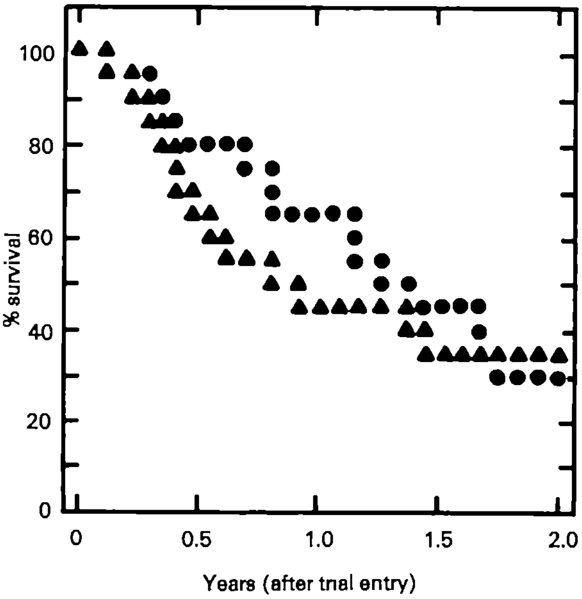

Fig. 1 Two-year crude survival rate in 54 eligible patients with metastatic renal carcinoma. ●● Interferon-alpha only (27) ▲▲ Interferon-alpha + vinblastine (27)

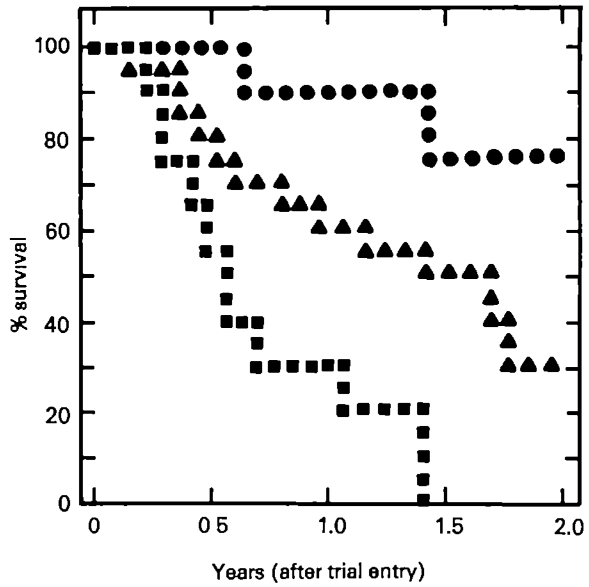

Fig. 2 Two-year crude survival rate in 49 patients with metastatic renal carcinoma treated with interferon-alpha ± vinblastine ●● Response (9), ▲▲ No change (29), $P<0.05$, ■■ Progression (11) $P<0.05$.

Toxicity

Flu-like symptoms (fatigue, muscle pain, fever) represented the most common side effect (Table 3), requiring the dosage of IFN to be modified/discontinued in 17 and 15 patients on treatments A and B respectively. Grade 3 leucopenia was seen only in patients in treatment group B. In 10 patients the VBL dosage had to be modified, mainly due to leucopenia. Approximately half of the patients developed an increase in serum gamma GT and ASAT during treatment. In addition to the side effects mentioned in Table 3, 1 patient on treatment A complained of visual disturbances. Retinal exudations were demonstrated. All side effects were reversible after discontinuation of treatment.

Table 3 Toxicity

	IFN (24)	*IFN+VBL (25)*	*Total (49)*
(A) Clinical			
Flu-like symptoms			
moderate	6	14	20
severe	11	4	15
Weight loss >5%	13	13	26
Neuropathy (Grade 3/4)			
central	1	1	2
peripheral	0	1	1
Skin (Grade 2)	1	2	3
IFN tolerance			
good*	9	12	21
fair†	7	9	16
poor‡	10	6	16
VBL modification		10	10
(B) Haematological, biochemical			
Nadir leucopenia			
Grade 1	9	7	16
Grade 2	6	7	13
Grade 3		6	6
Nadir thrombocytopenia			
Grade 1		1	1
Grade 2	1		1
Gamma GT elevation			
Grade 1	8	4	12
Grade 2	5	5	10
Grade 3/4	5	3	8
ASAT elevation			
Grade 1	7	8	15
Grade 2	1	4	5
Grade 3/4	5	1	6

*No dose modification.
†Dose reduction/delay
‡Permanent discontinuation of IFN.

Discussion

The overall response rate of 18% is within the confidence invervals of response rates reported by other workers investigating IFN in renal carcinoma (Quesada *et al.*, 1985; Krown, 1987; Muss *et al.*, 1987; Sarna *et al.*, 1987; Trump *et al.*, 1987). In agreement with Neidhardt *et al.* (1987), we found similar response rates for IFN and IFN+VBL. Bergerat *et al.* (1988) observed a 42% response rate with combination treatment but the patients received higher doses of IFN than those used in the present study. A higher IFN dose may also be the reason for a 33% response rate following combination treatment in an earlier phase II study (Fosså *et al.*, 1986). The present results, together with previously published observations, suggest that any superiority of IFN+VBL remains doubtful when compared with IFN alone. Future phase III studies are necessary to prove or disprove the superior response rates claimed for combination treatment.

The range and degree of toxicity were similar to those found in previous studies. The flu-like symptoms were the most important clinical side effect and the dosage of IFN frequently had to be modified. This toxicity may be reduced by simultaneous administration of corticosteroids, thus permitting long-term IFN treatment (Fosså, 1987).

The efficacy of IFN+corticosteroids in renal carcinoma should be evaluated clinically in a phase II study.

IFN (± VBL) should be regarded as the treatment of choice in metastatic renal carcinoma and patients who are suitable for medical treatment should be offered a 2-month trial with interferon. Most of the responding patients can be identified at that time due to a significant reduction in tumour size, although not all will fulfil the strict criteria of PR or CR. Individual patients may experience a clinically satisfactory, long-lasting remission which may continue after cessation of treatment. However, this does not prove *per se* that IFN increases the survival of responding patients, as they may have a biologically less aggressive disease which would lead to long-term survival even without IFN. The 1-year crude survival rate for all 54 eligible patients in this study was similar (about 50%) to that from a previous study in patients not receiving IFN (Fosså *et al.*, 1975).

It is concluded that IFN has an anti-tumour effect in metastatic renal carcinoma, yielding response rates of 15 to 20%. Whether the combination of IFN and VBL yields an even higher response rate is not known. Flu-like symptoms often lead to intolerance of treatment and reduction in dosage. New regimes should, therefore, be tried, *e.g.* the combination of IFN and corticosteroids.

Acknowledgement

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The Fine Structure of Human Pseudomembranous Trigonitis

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Summary—The present investigation provides a histological and fine structural description of pseudomembranous trigonitis, an ill-understood metaplastic condition affecting particularly the female trigone. Normal trigonal urothelium consists of 3 cell layers (basal, intermediate and superficial), whereas pseudomembranous trigonitis constitutes many layers of stratified squamous epithelium. The basal cells contain prominent nuclei with condensed chromatin, nucleoli and nuclear bodies. The cytoplasm of these cells is rich in mitochondria. The profiles of the urothelial cells become progressively elongated, their nuclei increasingly smaller and their content of cell organelles gradually reduced as the luminal surface is approached. The squamous surface cells, linked by desmosomes, retain many longitudinally arranged fine filaments, together with an occasional degenerate nucleus. The mitotic index of pseudomembranous trigonitis is 0.17% (SD 0.09%), *i.e.* significantly higher than normal (0%).

Pseudomembranous trigonitis represents a poorly documented and understood condition commonly affecting the female trigone. Defined as a partial or complete replacement of urothelium by mature squamous epithelium, it is diagnosed endoscopically by the presence of a white patch or plaque visible on the trigone (Henry and Fox, 1971). This condition was first described as "cystitis trigoni" by Heymann (1905) and was believed to consist of a true epithelial membrane (Cifuentes, 1947). The condition has been synonymously called vaginal metaplasia of the trigone, urethro-trigonitis, or squamous metaplasia of the trigone (Koss, 1975). Squamous metaplasia detected elsewhere in the bladder is often termed leukoplakia, or "atypical" squamous metaplasia. The malignant potential of leukoplakia, in terms of progression to squamous cell carcinoma, has long been recognised (Walts and Sacks, 1977; Bensen *et al.*, 1984; Mueller *et al.*, 1987). It is not clear whether pseudomembranous trigonitis should be considered a normal variant of trigonal urothelium in women. Performing autopsies of macroscopically normal bladders, Wiener *et al.* (1979) detected vaginal or squamous metaplasia in 40% and 5% of female and male trigones respectively.

Since the fine structure and aetiology of pseudomembranous trigonitis are unknown, the present study, part of a comprehensive investigation of human urothelial morphology, intended to provide a detailed description of this condition. The latter findings were confirmed by clinical and urodynamic data, and controlled with trigonal urothelium judged endoscopically to be normal (Jost, 1988; Jost *et al.*, 1989).

Patients and Methods

Clinical Data. Biopsies from the mucosa of the human urinary bladder were obtained from 4 female patients undergoing diagnostic or review cystoscopy following their clinical presentation with suprapubic ache, frequency, stress incontinence, or to investigate further the aetiology of haematuria (Table). Cystoscopy was carried out after informed consent by all patients, under general anaesthesia; pre-medication was administered by joint oral application of diazepam and cyclizine,

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Table Patients with Pseudomembranous Trigonitis

No.	*Sex*	*Age*	*Occupation*	*Smoker*	*Alcohol*	*Symptoms*	*Cystoscopy*
1	F	22	Retail manager	No	—	Recurrent cystitis, dysuria, haematuria, stress incontinence	Pseudomembranous trigonitis
2	F	33	Housewife	No	No	Suprapubic discomfort	Distal pseudomembranous trigonitis
3	F	44	Machine operator	2/day	Some	Pain at the site of previous hysterectomy	Pseudomembranous trigonitis, slight petechial bleeding
4	F	44	Domestic worker	5/day	Some	Haematuria	Early pseudomembranous trigonitis
			(3 months later, no further haematuria)	(past smoking 40/day)			

induction by intravenous injection of sodium thiopentone, and maintenance of anaesthesia by nitrous oxide, oxygen and halothane. Cystoscopy involved irrigating the urinary bladder with 200 ml isotonic 1.5% glycine to assess the organ macroscopically. The presence of pseudomembranous trigonitis was diagnosed and small cup biopsies were removed from the trigonal area of the urinary bladder with a cystoresectoscope (Carl Storz endoscope equipped with a 30° telescope and cold cup biopsy forceps).

Tissue Preparation for Light and Electron Microscopy. To avoid fixation artefacts, the exposure time to the irrigation fluid was minimal (1–2 min). Biopsies were fixed immediately upon removal from the urinary bladder in 2.5% glutaraldehyde (in 0.1M sodium cacodylate buffer at pH 7.3), first at room temperature for 2 h, then stored at 4°C for a minimum of 24 h. After fixation, specimens were diced into 1 to 2 mm cubes, washed for 15 min in 0.1M sodium cacodylate buffer (at pH 7.3), and post-fixed for 1 h in 1% osmium tetroxide, made up with the same buffer (10 min). Tissue was subsequently immersed in a 2% aqueous solution of uranyl acetate (15 min), dehydrated and embedded in epoxy resin. Thick sections (1.5 μm) were stained for light microscopy with 1% toluidine blue. Thin sections (80–90 nm) were double-stained (5 min each) with alcoholic uranyl acetate and 0.3% lead citrate, prior to examination in a transmission electron microscope.

Mitotic Activity. The incidence of urothelial mitotic figures (mitotic index, in %) was recorded in resin-embedded histological sections (1.5 μm thick) of pseudomembranous trigonitis and of normal urothelium from the bladder and trigone. At least 4 patients were included for each category. Mitotic figures were confined to the basal region of squamous metaplastic urothelium, *i.e.* observed either in the basal layer or in the 1–2 layers closest to the basal layer (Fig. 1). A minimum of 2000 urothelial cells from this region were scored per patient.

Results

Analysis of Patients. Four female patients were cystoscopically diagnosed as having pseudomembranous trigonitis (Table). Their average age was 35.8 years (SD 10.5), which is not significantly different from that of the patient population with normal trigonal urothelium (Jost, 1988; Jost *et al.*, 1989); 2 patients smoked and drank alcohol and 2 presented with haematuria or pain/suprapubic discomfort respectively.

Light Microscopy. In pseudomembranous trigonitis, the trigonal urothelium displayed the characteristic morphology of squamous metaplasia, *i.e.* the presence of multilayered (stratified) squamous cells. Squamous metaplastic urothelium consisted of numerous layers, a combination of nucleated and

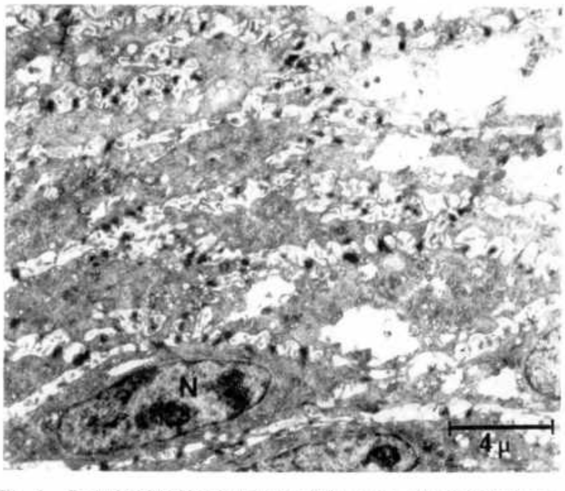

Fig. 1 Pseudomembranous trigonitis: zone of lower intermediate cells assuming squamoid shapes.

non-nucleated cell layers, arranged in strata from base to surface (Fig. 2). The basal region was 2 to 3 cells in thickness and consisted of the smallest cells of the epithelium. The nucleus occupied a large proportion of each cell. In general, the shape of cells in this basal region was cuboidal or columnar. Accordingly, their nuclei assumed more rounded or more elongated configurations. Above the basal region the urothelial cells appeared increasingly squamous in shape, their long axis being orientated parallel to the base of the urothelium (Fig. 2). More superficial cells appeared non-nucleated and the squamous stratification became especially marked. The most superficial cells generally lacked a nucleus and possessed pale-staining cytoplasm. The number of rows of squamous cells was difficult to estimate.

Mitotic Activity. Squamous metaplasia was accompanied by a significant rise in the urothelial mitotic index from 0% (SD 0%) for normal urothelium to 0.17% (SD 0.09%) for pseudomembranous trigonitis.

Transmission Electron Microscopy. The basal lamina consisted of an electron-dense lamina densa and an electron-lucent lamina rara, the latter being adjacent to the basal cell membrane. Basal cells varied in shape from cuboidal to slightly flattened, and their cytoplasm, rich in mitochondria, varied in its electron density (Fig. 3). Presumptive lysosomes were rarely observed. Small intercellular spaces occurred between the cells of the basal and immediately adjoining suprabasal layers (the basal region), while interlocking cytoplasmic processes were common (Figs 1 and 3). The nuclei in the bsasal region contained highly condensed chromatin, nucleoli and nuclear bodies. The profiles of the urothelial cells became progressively elongated and their nuclei increasingly smaller as the luminal surface was approached. Many of the more superficial cells lacked a nucleus and there was a gradual reduction in their content of cell organelles towards the luminal surface (Figs 4 and 5). The squamous surface cell layers rarely retained a nucleus, which, when present, was of a degenerate appearance (Fig. 6). Metaplastic cells closest to the luminal surface therefore appeared to be dead or dying, but retained their parallel orientation to the basal lamina. Their cytoplasm contained many fine filaments arranged longitudinally, while the cells were linked together by desmosomes. The membranes of the surface cells appeared to maintain their structural integrity, thereby forming an elaborate network between adjacent and sub-superficial metaplastic cells. Squamous surface cells may appear smooth or folded.

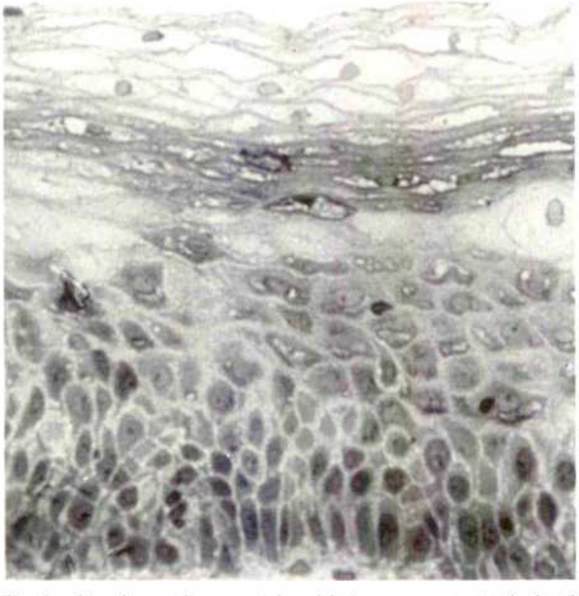

Fig. 2 Pseudomembranous trigonitis (squamous metaplasis of the female trigone): the largely cuboidal cells of the basal cell zone become increasingly enucleated and squamoid towards the luminal surface. (Toluidine blue ×650).

Discussion

In pseudomembranous trigonitis, or squamous metaplasia of the trigone, trigonal urothelium

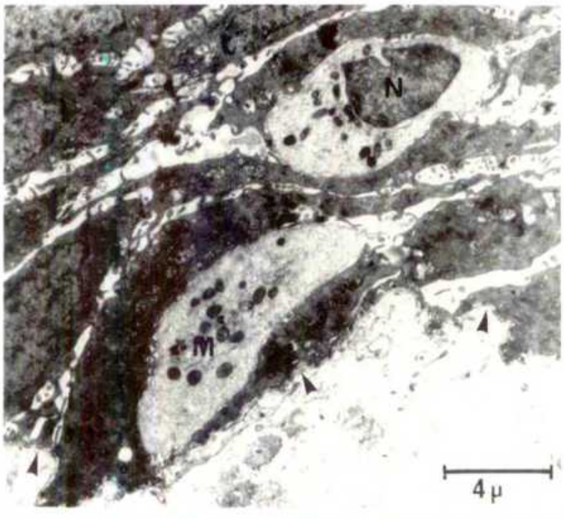

Fig. 3 Pseudomembranous trigonitis (squamous metaplasia of the female trigone): basal cell layer delineated by a basal lamina (arrows). Basal cells can be either rather electron-lucent or more electron-dense, and each contains groups of mitochondria (M) and a nucleus (N) with condensed chromatin.

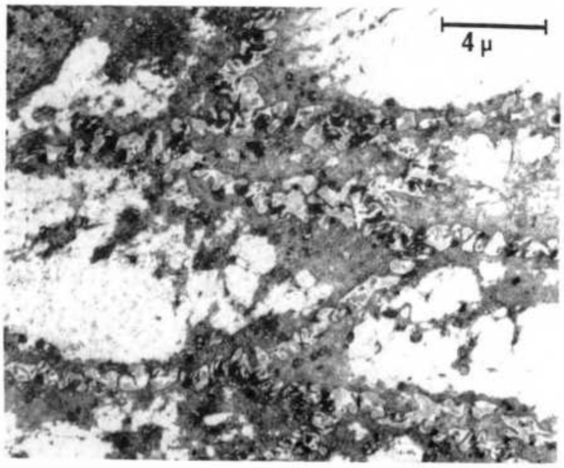

Fig. 4 Pseudomembranous trigonitis: cells situated more basally to those shown in Figure 5. Urothelial cells are linked by interdigitating cytoplasmic processes.

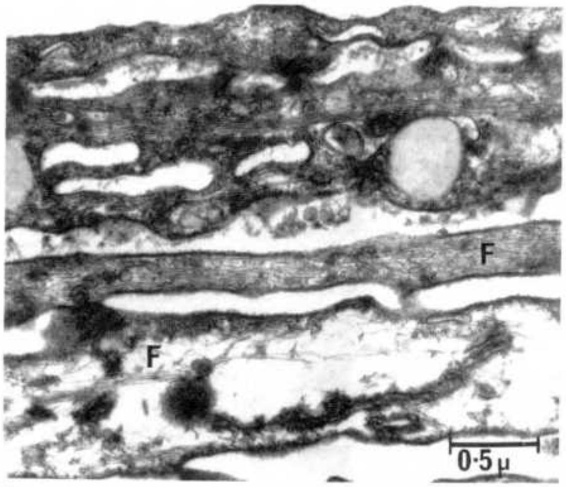

Fig. 6 Pseudomembranous trigonitis: surface cells consisting of flattened layers of cytoplasm, poor in organelles and rich in filaments (F).

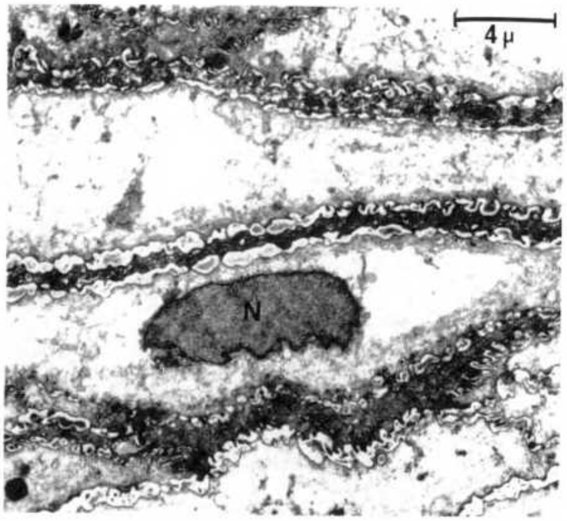

Fig. 5 Pseudomembranous trigonitis: the cellular organisation of the urothelium is stratified squamous. As confirmed by serial sections, occasional nuclei (N) are visible inside some of the urothelial cells only. Cells appear electron-lucent and increasingly devoid of organelle content as the luminal surface is approached.

displays a different end-point of differentiation, namely the presence of stratified squamous cells. This change in differentiation renders trigonal urothelium morphologically similar to epidermal or vaginal epithelium. The clinical significance of pseudomembranous trigonitis is still under debate. In premenopausal women, the condition appears to correlate with frequency and urgency symptoms (Henry and Fox, 1971; Murakami *et al.*, 1985). Starklint *et al.* (1976) examined 40 primary urothelial carcinomas and found squamous metaplastic areas in 24 tumours. They did not specify from which region(s) of the bladder their material originated. Brawn (1984) suspected, without further evidence or elaboration, that squamous metaplasia appears to be less efficient in maintaining the barrier between blood and urine than normal urothelium. If true, the area of the bladder affected by squamous metaplasia would be more exposed to potentially hostile urine-borne substances, which in turn could participate in causing (further) urothelial disease.

It is an interesting speculation whether squamous metaplasia represents a complete change in cell differentiation, or whether it is an expression of hyperactivity of existing cell mechanisms (Hicks, 1975). The former would be a largely qualitative change, involving the generation of new molecular species, whereas the latter would be a predominantly quantitative event, involving increased production of existing molecules. Koss (1977) concluded that the role of squamous metaplasia in experimental bladder cancer (of the rat) deserved further exploration. In his experimental system, squamous metaplasia appeared to be the most important trigger in the formation of invasive carcinoma (Koss, 1977). In the human, squamous metaplasia requires careful medical follow-up, because it may lead to squamous cell carcinoma with an unknown frequency (Koss, 1975). Squamous cell carcinoma has a poor prognosis, and in parts of Africa and the Middle East it is associated with the problem of bilharzial cystitis (Hicks, 1975, 1983). Koss (1975) drew a conceptual distinction between "true squamous metaplasia", which he stated was rarely confined to the trigone and harboured considerable carcinogenic potential, and squamous metaplasia of the trigone or pseudomembranous trigonitis, which, in women, was probably a urothelial variant developing under hormonal impact (Koss, 1975, 1985). In their post mortem study, Wiener *et al.* (1979) reported pseudomembranous trigonitis to be present in 40% of adult women, but in only 5% of adult men. Widran *et al.* (1974) linked the occurrence of pseudomembranous trigonitis in men with prostate disease. Koss (1985) suspected that the presence of squamous trigonal urothelium in women may account for the cyclic changes in the squamous cells in the urinary sediment of ovulating women. Mostofi and Davis (1984) stated that squamatisation of the trigone is a common occurrence in women during oestrogen production. Tyler (1962), investigating autopsy cases and female trigonal biopsies, did not observe any pseudomembranous trigonitis in stillbirths, newborns and children, despite the high maternal oestrogen stimulation. This author thus concluded that oestrogen cannot be entirely responsible for pseudomembranous trigonitis. However, cyclic changes corresponding to the menstrual cycle did occur. Tyler (1962) claimed that during menses many of the superficial layers are shed, but provided no details on the remaining number of urothelial cell layers. Furthermore, no cases of pseudomembranous trigonitis were found before the menarche, and there was a declining incidence after the menopause.

The ultrastructural features associated with pseudomembranous trigonitis clearly highlight the progressive, suprabasal differentiation of the tissue into a stratified squamous type. Squamous metaplastic cells undergo terminal differentiation: they are without nuclei, are relatively devoid of intracellular organelles and are flattened in shape. It is noteworthy, however, that terminally differentiated squames continue to be linked by desmosomes and contain fine filamentous material, probably of intermediate type. The retention by the upper strata of some internal cytoskeleton, as well as external membranous and desmosomal connections, might be functionally important to retain some of the blood/urine barrier provided by normally differentiated, 3-layered trigonal urothelium (Jost, 1988). Compared with normal urothelium of the bladder or trigone, there is evidence of significantly enhanced proliferative activity in pseudomembranous trigonitis, as shown by a mitotic index of 0.17% (SD 0.09%). As squamous metaplastic tissue is organised in more strata than normal trigonal or non-trigonal urothelium, the observed increased proliferation of the tissue is likely to be linked to, or required by, its altered pattern of differentiation.

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Is the Treatment of Urgency Incontinence a Placebo Response?

Results of a Five-year Follow-up

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Summary—The treatment and symptomatic outcome were reviewed in 50 women who had presented with urgency incontinence as their main symptom 5 years previously. All had idiopathic urgency incontinence and, on the basis of urodynamic investigation, 40 were considered to have detrusor instability and 10 sensory urge incontinence. The results indicate that the natural history of sensory urgency is one of spontaneous resolution; all treatments of detrusor instability (including surgery) produced an unsustained short-term symptomatic response. This pattern of response to therapy may be interpreted as being largely of a placebo nature and this emphasises the need for long-term follow-up in the assessment of new treatment modalities.

Urgency incontinence in women is distressing not only for the patient but also for the urologist trying to treat it. Patients with a urinary tract infection or a bladder calculus are easily treated and discharged. However, patients with idiopathic urgency incontinence of motor or sensory type form a large and often vociferous group of regular out-patient attenders.

The treatment of idiopathic urgency incontinence falls into 3 main categories. (1) Psychological therapy such as bladder retraining based on the principles of biofeedback (Cardozo *et al.*, 1989). (2) Pharmacological agents, with a variety of anticholinergic preparations designed to reduce detrusor contractility. (3) Surgical manoeuvres aimed at augmenting bladder capacity and reducing the efficacy of detrusor contractions, or selective denervation (Bramble, 1982; Ewing *et al.*, 1982; Mundy and Stephenson, 1985). Surgical treatment of this type is normally reserved for patients with intractable detrusor instability.

Controlled clinical trials of drug therapy have confirmed a large placebo response in the treatment of urgency incontinence, and the efficacy of certain surgical treatments for detrusor instability has been challenged (Walter *et al.*, 1982; Meyhoff *et al.*, 1983; Wall and Stanton, 1989). Our clinical impression suggested that a proportion of patients failed to obtain long-term benefit despite intensive treatment, and this prompted a retrospective review.

Patients and Methods

A retrospective review was performed of the period between 1982 and 1983 which identified 50 women referred to the urology out-patient department with idiopathic urgency incontinence as their main presenting symptom and diagnosis. All patients had had a detailed clinical history and examination, blood analysis, MSSU, IVU and cystoscopy in order to exclude those with incontinence secondary to infection, stone or tumour.

All patients were further investigated with a 4-week micturition diary and filling cystometry to identify the first desire to void, the volume at first unstable wave, and the maximum cystometric capacity. Urodynamic evaluation was performed using the DISA 2000 system. Medium fill cystometry was performed with the patients in the sitting position using Statham transducers.

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Patients still attending the out-patient clinic were interviewed and an assessment made of their current symptomatology. The patients who were not attending the out-patient clinic were sent a questionnaire requesting details of current symptoms and drug therapy; in addition, patients were offered the opportunity for a review at the out-patient clinic.

A subjective analysis of the 4 main symptoms (urgency, urge incontinence, frequency and enuresis) of bladder instability was made. Patients were classified as having 1 of 3 possible outcomes:

(1) Unchanged—no improvement of any symptoms.
(2) Modified—improvement of some but not all symptoms.
(3) Resolved—all symptoms resolved.

Results

Nineteen patients were still under review at the urology clinic and 7 had been discharged. Twenty-four had been lost to follow-up because they had failed to attend for return appointments; 22 of these patients replied to the questionnaire and 15 attended the clinic for review. No follow-up was obtained from 9 patients, 2 of whom had died in the interim from ischaemic heart disease. Full follow-up was therefore available on 41 patients.

On the basis of the initial urodynamic findings, patients were divided into 2 groups: motor urge incontinence and sensory urge incontinence. Detrusor instability was interpreted according to the ICS definition of an uninhibited contraction > 15 cm of water (Bates *et al.*, 1976). Of the 41 patients with complete follow-up, 33 had motor urge incontinence and 8 sensory incontinence.

The age of the 33 patients with motor urgency ranged from 16 to 62 years (mean 42.3) compared with the sensory group (range 28–50 years, mean 40.1).

The results of filling cystometry demonstrated a significantly higher volume at the first desire to void in the sensory group (range 48–210 ml, mean 85); in the motor group the range was 15 to 200 ml (mean 43) ($P<0.05$). The maximum bladder capacity in the sensory group ranged from 134 to 465 ml (mean 320) compared with the motor group (range 48–355 ml, mean 185) ($P<0.02$).

A summary of the different therapies undergone by the patients is shown in Tables 1 and 2. The symptomatic outcome at 5 years is shown in Table 3. Although 56% of the patients were symptomatically unchanged at 5 years, 83% showed some temporary symptomatic benefit. The difference in the duration of this symptomatic improvement in relation to the type of treatment is illustrated in Table 4.

Table 1 Summary of Treatment

Changes in drug therapy	129
Bladder retraining	15
Bladder distension	10
Operative procedures	14
(Bladder transection—endoscopic or open)	

Table 2 Drug Treatments

Emepronium bromide
Probantheline
Terodiline
Flavoxate hydrochloride
Imipramine

Table 3 Symptomatic Outcome at 5 Years

Unchanged	23 (56.2%)		
Modification of symptoms	8 (19.5%)		
Resolved	10 (24.3%)	Motor	4 (12%)
		Sensory	6 (75%)

Table 4 Duration of Symptomatic Improvement

Type of treatment	*Median time of response (months)*
Pharmacology/biofeedback	3
Helmstein's	4
Bladder transection	6

Discussion

Interpretation of the outcome of any treatment for urgency incontinence is complex. The natural history is unknown and a high placebo response has been consistently shown (Walter *et al.*, 1982; Meyhoff *et al.*, 1983). Although retrospective, the numbers in this study compare favourably with those in trials of therapy for this condition (Bramble, 1982, Ewing *et al.*, 1982; Gerstenberg *et al.*, 1986; Wall and Stanton, 1989). The patients in this study were selected only by their principal presenting symptom and treatment was therefore heterogeneous. This represents urgency incontinence as encountered by the urologist in the out-patient clinic.

The results suggest that the division of urgency incontinence into motor and sensory types by urodynamic parameters has important prognostic implications, since 75% of patients with sensory urgency were symptom-free at 5 years but only 12% with motor urgency were symptom-free.

This may be interpreted in 2 ways: either treatment is effective for sensory urgency, or the natural history is one of spontaneous resolution. Analysis of the records of patients with sensory urgency showed that all were treated pharmacologically or by bladder retraining; 34 patients (83%) showed a pattern of initial response to therapy followed by relapse. A change in pharmacological agent again resulted in symptomatic improvement, again followed by relapse. Of those patients symptom-free at 5 years only 16% were on therapy.

A similar pattern of initial response and subsequent relapse was encountered in the detrusor instability group. The duration of symptomatic improvement in these patients was related to the nature of the therapy; the more invasive the treatment the longer the period of improvement reported by the patient (Table 4). This suggests either that detrusor instability is a disease that becomes refractory to treatment or that much of the response is of a placebo nature.

This retrospective study also identified a high non-attendance rate (45%) in patients with detrusor instability. In contrast to the sensory urgency group, this was not because of a spontaneous improvement, as all of these patients had continuing symptoms. Patients were offered an opportunity for further treatment but only 20% accepted. Why patients with continuing symptoms should refuse further therapy is difficult to ascertain. A few indicated that they had "come to terms" with their urgency incontinence. It would appear that the others had become disillusioned with the treatment offered.

Several forms of treatment have been proposed, based on the results of short-term follow-up (Ramsden *et al.*, 1976; Cardozo *et al.*, 1978; Ewing *et al.*, 1982). Subsequent studies from other centres have failed to reproduce the symptomatic benefit claimed by the original authors (Pengelly *et al.*, 1978; Ferrie *et al.*, 1984; Wall and Stanton, 1989).

This study has indicated that any form of treatment for detrusor instability results in a temporary improvement in symptoms which may last for 6 months, To demonstrate the conclusive benefit of treatment of urgency incontinence requires a follow-up in excess of 6 months.

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Comparison of Stamey and Pereyra-Raz Bladder Neck Suspensions

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Summary—Endoscopic bladder neck suspension has become one of the more popular methods of surgical treatment of stress incontinence. The Pereyra technique was first described in 1959 and modified by Raz in 1981. Stamey first described his technique in 1973 and this has been modified in a number of ways. The reported cure rates are 54 to 94% for the Pereyra-Raz procedure and 61 to 92% for the Stamey procedure.

We present a comparative review of the technical results of treatment of 30 patients with a modified Stamey procedure and 17 patients with a modified Pereyra-Raz technique. The age range of the 2 groups was comparable. A successful result, with either complete continence or only minor occasional leaks after surgery, was achieved in 80% with the Stamey techniques and 76% with the Pereyra technique. Those patients not helped by the procedure had nearly all undergone previous surgery for incontinence. The Pereyra technique was used more frequently in patients who had failed previous incontinence surgery (including the Stamey technique). Complications were minor; 5 buffer infections occurred (3 buffers were removed).

Both techniques offer a significant improvement in continence, but previous surgery is associated with a higher failure rate.

The Pereyra bladder neck suspension was first described in 1959 and its modification by Raz in 1981. Stamey first described his technique in 1973. This study attempts to compare the results of the 2 procedures.

The reported cure rates are 61 to 92% for the Stamey procedure (Stamey, 1980; Mundy, 1983; Handley Ashken *et al.*, 1984; Richardson *et al.*, 1984; Spencer *et al.*, 1987; Jones *et al.*, 1989) and 54 to 94% for the Pereyra-Raz procedure (Leach and Raz, 1984; Riggs, 1986; Mäkinen *et al.*, 1987). It is agreed by most workers that the effectiveness of the 2 procedures is due to intra-abdominal replacement of the urethra, thereby restoring proper urethral support with restoration of the positive pressure transmission to the proximal urethra. There is disagreement regarding change in the functional length of the urethra (Leach *et al.*, 1987; Massey *et al.*, 1987).

Patients and Methods

A retrospective review was undertaken of 47 patients treated by endoscopic bladder neck suspension in the St Peter's Hospital Group by P.J.R.S. over a 3-year period. All patients were assessed clinically and all but 2 had pre-operative video-urodynamic studies. All procedures were performed under general anaesthesia with broad spectrum antibiotic cover. In the case of the Stamey procedure a number 1 nylon ligature was passed from the vagina suprapubically with a double pronged ligature carrier passed from below upwards, initially using Dacron vaginal buttresses as described by Mundy (1983), but subsequently silicone to reduce the infection rate. These sutures were tied over the rectus sheath with silicone buffers via separate small suprapubic incisions. In the case of the

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Pereyra-Raz procedure, bilateral vertical paraurethral incisions were made and the plane between the vagina and peri-urethral fascia was entered. The retropubic space was then entered by blunt and sharp dissection and the endopelvic fascia freed from its attachments from the level of the pubic bone to the ischial tuberosity. The sutures were anchored by taking 3 bites, in helicoidal fashion, of the vaginal wall (but not mucosa), pubocervical fascia and the medial end of the endopelvic fascia, with number 1 nylon (Raz, 1981). The sutures were passed with a double pronged ligature carrier as described above but with fingertip guidance through the retropubic space to reduce the chance of inadvertent penetration of the bladder. The sutures were tied separately over silicone buffers via suprapubic incisions as in the Stamey procedure.

In both procedures a single cystoscopy was usually all that was necessary prior to tying the sutures to check that they had not penetrated the bladder and that bladder neck elevation was satisfactory. At the end of the operation a vaginal pack was inserted and a Stamey suprapubic catheter left *in situ*. This catheter was clamped on the third post-operative day and removed when residual urine was less than 50 ml. Patients were followed up in out-patients but follow-up video-urodynamic tests were performed only when clinically indicated. All operations were performed by one surgeon.

Results

Thirty patients had the Stamey operation and 17 the Pereyra procedure (including 3 whose Stamey operation had failed). The age range for the Stamey group was 32 to 65 years (mean 49.4) and for the Pereyra group 34 to 67 years (mean 48.7). Follow-up ranged from 2 months to 2½ years.

Sixteen Stamey patients and 9 Pereyra patients had undergone previous anti-incontinence surgery. In addition, 3 Stamey and 3 Pereyra patients had undergone a hysterectomy only.

Three Stamey patients had detrusor instability pre-operatively. Post-operatively 1 was dry, 1 was partially dry with symptoms of urgency and urge incontinence and 1, although dry, was troubled by persisting frequency and urgency. The latter 2 patients underwent clam ileocystoplasty for their symptoms. Three Pereyra patients were unstable and post-operatively 1 was dry and 2 failed. None of the patients who had post-operative video-urodynamic studies developed instability that was not present pre-operatively. Seven patients (3 Pereyra, 4 Stamey), who were urodynamically stable pre-operatively, complained of some urgency and/or urge incontinence post-operatively; 4 required no treatment and 3 improved with terodiline.

Complications were infection of the buffers, 4 in the Stamey group (13%) and 1 in the Pereyra group (6%) and bleeding from the vaginal incisions in 2 Pereyra patients (12%). In the Stamey group 3 patients with infection required removal of the buffers (2 bilaterally) and 1 required excision of granulation tissue. The Pereyra patient settled on antibiotic treatment but developed further incontinence despite good elevation of the bladder neck. No patient developed incontinence as a result of buffer removal. Both patients with bleeding settled after packing the vagina and they remained continent. In 3 patients the right medial suture penetrated the bladder and in each case this was rectified without consequence.

No patient required prolonged catheterisation, although 2 patients with large acontractile bladders who were on intermittent self-catheterisation had to continue this post-operatively. The average length of hospital stay was 5 days.

Fifteen patients in the Stamey group were cured (50%), 9 were improved (30%) and 6 failed (20%) (Table 1). Of the failures, 1 had a colposuspension, 4 had a Pereyra procedure (2 cured, 2 failed, of whom 1 had a colposuspension) and 1 was cured after a further Stamey operation. Eleven Pereyra patients (65%) were cured, 2 improved (12%) and 4 failed (23%) (Table 2). Of the failures, 1 had a colposuspension and 1 was practising vaginal weight training.

Table 1 Previous Gynaecological Surgery: Stamey Procedure

	Cured	*Improved*	*Failed*
Previous surgery	7	3	6
Hysterectomy only	1	2	0
No previous surgery	7	4	0
Total	15 (50%)	9 (30%)	6 (20%)

Table 2 Previous Gynaecological Surgery: Pereyra Procedure

	Cured	*Improved*	*Failed*
Previous surgery	4	2	3
Hysterectomy only	3	0	0
No previous surgery	4	0	1
Total	11 (65%)	2 (12%)	4 (23%)

There was only 1 failure (in the Pereyra group) in a patient who had undergone no previous anti-incontinence surgery. All of the other failures were in patients who had undergone previous surgery.

Discussion

Since Pereyra first described needle bladder neck suspension there have been a number of modifications (Siegel and Raz, 1988), the best known being the Stamey operation. The advantages of simplicity and a shorter hospital stay have contributed to the popularity of these procedures compared with open colposuspension for the treatment of female stress incontinence. Unfortunately, subsequent workers have not always succeeded in reproducing Stamey's high success rate. One potential weakness of the Stamey technique is that the integrity of the repair relies upon Dacron buttresses placed through the pubocervical fascia. These buttresses are placed superficially beneath the vaginal skin and are therefore liable to infection; rates vary from 6 to 16% (Stamey, 1980; Mundy, 1983). Secondly, because of the flimsy nature of the pubocervical fascia, the buttresses have a tendency to cut through. In the Raz modification of the Pereyra procedure, the greater dissection allows for adequate mobilisation of the urethra, bladder and vaginal wall. This enables elevation of the bladder neck and tying of the sutures without tension. The anchorage of the sutures is such that buttresses are not needed. The use of a double pronged ligature carrier reduces the number of needle passages from 4 to 2 and also provides a 1-cm bridge over which the sutures are tied.

Our results show that both procedures are effective and have a low complication rate. In patients who had not undergone previous surgery for incontinence, 7/8 in the Pereyra group and 14/14 in the Stamey group were either cured or improved. This confirms that endoscopic bladder neck suspension is the procedure of choice in such patients. In patients who had undergone previous surgery for incontinence, 6/9 (66%) in the Pereyra group and 10/16 (63%) in the Stamey group were either cured or improved.

The relationship between stress incontinence and detrusor instability is complex (McGuire, 1988). It has been shown that some women develop detrusor instability after surgery for stress incontinence. This may be the result of an increase in outflow resistance after the procedure. It is also possible that detrusor instability may be difficult to detect pre-operatively in the presence of severe stress incontinence. Of the patients in this study shown to be unstable pre-operatively, 2 had persisting symptoms of instability post-operatively and therefore underwent clam cystoplasty. Post-operative urodynamic tests were done only when symptoms indicated and no new instability was demonstrated. Terodiline was effective in relieving symptoms of urgency and urge incontinence. It is advisable to warn patients who complain of urgency and urge incontinence that these symptoms may not be helped by surgery and may in fact worsen post-operatively. In patients with detrusor instability and stress incontinence there is a place for endoscopic bladder neck suspension prior to bladder augmentation surgery, although the increased outflow resistance may make intermittent self-catheterisation necessary.

In conclusion, both Pereyra-Raz and Stamey procedures are effective and the former has a slightly higher complete cure rate. Previous surgery is associated with a higher failure rate. The Pereyra-Raz technique has a lower complication rate and may have advantages in cases where other operations have failed or the pelvic fascia is weak.

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Bile Acid Malabsorption: a Complication of Conduit Surgery

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Summary—We examined the possibility that use of a section of the terminal ileum for ileal conduit construction may impair bile acid absorption and cause choloretic diarrhoea. Nineteen normal subjects (mean age 41 years) and 16 patients with conduits (mean age 47 years) were investigated using the SeHCAT retention test. Conduit patients showed significant impairment of SeHCAT retention compared with normal subjects; 82% of patients had a retention below the lower limit of normal. The mean bowel frequency of patients during the test was 3 motions/day this being significantly different from their pre-operative bowel habit. It was concluded that the use of the terminal ileum in conduit construction may impair bile acid absorption, as measured by the SeHCAT retention test, and may cause an increase in bowel frequency.

The ileal loop urinary conduit has been a popular procedure for the provision of urinary diversion since its description by Bricker (1950). It has commonly been used in the management of both malignant and benign bladder disease in all age groups. A number of complications are now recognised, including stomal stenosis and upper tract dilatation (Shapiro *et al.*, 1975; Dunn *et al.*, 1979; Orr *et al.*, 1981). Urinary stones, considered to result from urinary stasis and infection, occur in 4 to 18% of patients (Dunn *et al.*, 1979; Graham, 1982). Despite well documented follow-up, no specific gastrointestinal complications have been noted to result from the use of a portion of the ileum in conduit construction.

A number of considerations dictate the length and portion of ileum used in any individual patient, but typically a resection of at least 15 cm is taken from within the last 30 cm of small bowel. While such limited small bowel resection is usually insignificant, it now seems possible that the particular site used in conduit construction may influence functions specific to this area, notably that of bile acid absorption.

23-selena 25 homotaurocholic acid (SeHCAT) is a synthetic bile acid containing the gamma emitting isotope selenium 75. This label makes it possible to measure whole body turnover of taurocholic bile acid either by whole body counting (Nyhlin *et al.*, 1983) or uncollimated gamma camera counting (Thaysen *et al.*, 1982). SeHCAT has been shown to behave in the entero-hepatic circulation like natural taurine conjugated bile acids (Boyd *et al.*, 1981; Merrick *et al.*, 1982; Nyhlin *et al.*, 1983) and therefore, since absorption of taurine conjugated tri-hydroxy acids is almost exclusively due to active absorption in the terminal ileum, the rate of loss of administered SeHCAT from the body is a specific marker of terminal ileal function.

In this study the SeHCAT retention test (Thaysen *et al.*, 1982) was used to assess terminal ileal function in patients after conduit construction by comparison with results obtained in normal subjects. In addition, the influence of conduit construction on bowel frequency was assessed and the possibility that impaired terminal ileal function might be relevant in the development of renal stones.

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Patients and Methods

Two groups were examined:

(A) Normal subjects

The control group consisted of 8 males and 11 females, mean age 41.1 years (range 28–62). Excluded from the study were subjects with a history of current or past gastrointestinal symptoms and those with a bowel frequency in excess of 2 motions/day. For the purpose of this study a bowel habit exceeding 2 actions/day was considered abnormal.

(B) Study group

The records of all patients who had undergone conduit surgery by 1 urological surgeon (R.N.P.C.) were examined. Patients noted to have had chronic gastrointestinal symptoms, including bowel frequency in excess of 2 motions/day prior to surgery, were excluded, as were patients who had undergone radiotherapy as part of their management.

Three male and 13 female patients were examined. Their mean age was 46.8 years (range 27–63). The indications for operation are given in the Table. The mean time since operation was 5.5 years (range 2–12). The mean bowel frequency prior to operation was 1.3 actions/day. No patient had a history of urolithiasis.

Table Indications for Conduit Surgery

Bladder carcinoma	5
Multiple sclerosis	5
Idiopathic incontinence	6

All subjects attended the Department of Nuclear Medicine, having fasted for 4 h. A single capsule of SeHCAT (0.37 MBq) was given orally with a glass of water. After 4 h, anterior and posterior abdominal counts were taken over a 5-min period using an uncollimated Nuclear Data Radicamera peaked to 280 KeV using a 20% window. Patients were examined lying on a scanning couch with the camera 52 cm above the surface of the couch and centred over the umbilicus. Counts were corrected for background and the geometric mean of counts calculated:

$$\sqrt{(\text{Corrected anterior count} \times \text{corrected posterior count})}$$

Subjects returned for repeat counting after 7 days, the SeHCAT retention being calculated as:

$$\begin{array}{c}\text{Percent retention}\\ \text{of SeHCAT}\end{array} = \frac{\text{Geometric mean day 7}}{\text{Geometric mean day 1}} \times 100$$

All subjects maintained a record of daily bowel frequency during the study period, in addition to which 10 patients made a 24-h collection of urine for estimation of oxalate excretion.

Analysis

The mean 7-day SeHCAT retention for each group was calculated and comparison made using the Mann Whitney U Test. In the patient group, comparison between the pre-operative bowel frequency and that recorded during investigation was made using the Wilcoxon Test. Correlation analysis was performed between the result of the SeHCAT retention test and the recorded bowel frequency during the test using the Spearman Rank Correlation Coefficient, in order to explore the relationship between any impairment in terminal ileal function and the severity of bowel disturbance.

Urinary oxalate excretion was compared with the normal range for the clinical laboratory at Manchester Royal Infirmary (upper range of normal 0.32 mmol/24 h).

Results

The mean percentage retention of SeHCAT at 7 days was 31.5% in normal subjects (range 20–70%, SD ± 12.3) and 13% in the study group (range 1–39%, SD ± 10.6). The difference between groups was significant ($P<0.02$). Individual results are shown in Figure 1.

The distribution of pre- and post-operative bowel frequency in conduit subjects is illustrated in Figure 2. Mean bowel frequency before operation was 1.3 actions/day (range 1–2, median 1). Comparison of individual bowel frequency before and after operation using the Wilcoxon Test showed a significant difference ($P<0.01$).

A negative correlation ($rs = -0.65$) existed between the SeHCAT retention test result and the frequency of bowel habit during the examination (Fig. 3), there being a significant association between the 7-day retention and bowel habit ($P<0.02$).

Overall, 13 of the 16 patients (81%) had a SeHCAT retention below that of the normal subject group, but only 8 (50%) had a bowel frequency in excess of 2 motions/day; 7 patients (43%) had both a low SeHCAT retention and an excessively frequent bowel habit, as defined for this study.

Urinary oxalate excretion was normal in all

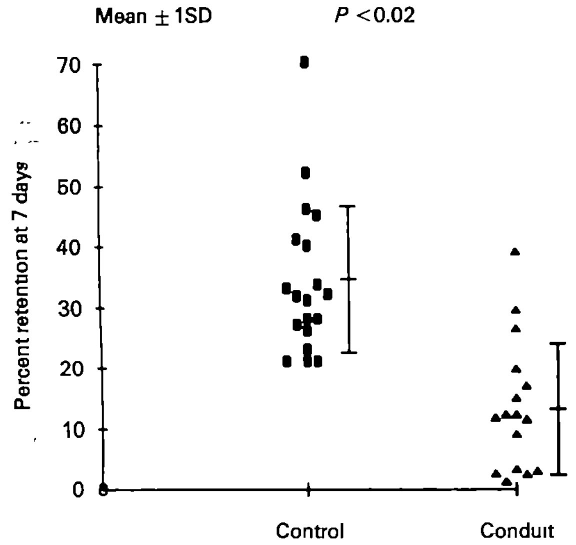

Fig. 1 Effect of conduit surgery on SeHCAT retention

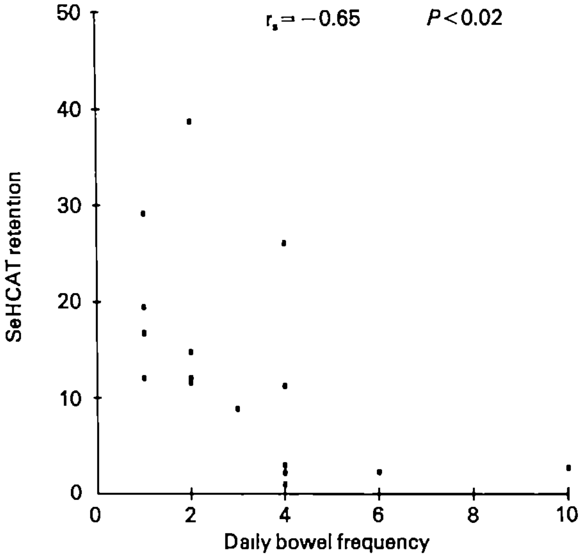

Fig. 3 Relationship of SeHCAT retention to bowel habit in patients after conduit surgery

patients studied (mean 0.17 mmol/24 h, range 0.08–0.29, SD ± 0.08), the mean SeHCAT retention in these patients being 13.5% (range 2–30%, SD ± 10.2).

Discussion

These results suggest that conduit surgery causes impairment of terminal ileal function and an increased rate of SeHCAT excretion from the body. Since SeHCAT has been shown to reflect the behaviour of natural conjugated bile acid in the enterohepatic circulation, this implies that conduit surgery leads to a reduction of active bile acid absorption and an increased loss of conjugated bile acid into the colon.

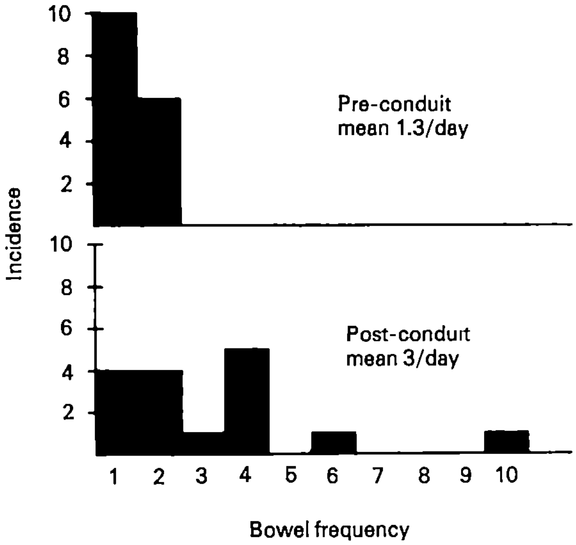

Fig. 2 Frequency of bowel habit before and after conduit surgery.

Unabsorbed conjugated bile acid entering the colon is deconjugated and dehydroxylated by bacteria to form secondary bile acids. Deoxycholic acid (the secondary bile acid of cholic acid) inhibits sodium and hence water reabsorption in the colon, the presence of excess deoxycholic acid resulting in diarrhoea (Dowling, 1982). It is possible, therefore, that the alteration in bowel habit observed in this study is the result of increased cholic acid loss into the colon, as reflected by reduced SeHCAT retention. It is apparent, however, that the wide range of results in both normal and patient groups requires that these results be substantiated by a prospective study of patients before and after surgery. An additional advantage of such a study would be the possibility of correlating the length and position of small bowel resection with the results of SeHCAT retention, since these data are not available in this retrospective study.

Given that the results do accurately reflect a trend to abnormal bile acid absorption, some assessment is required of the clinical relevance of such changes. If significant malabsorption is considered to be the association of an abnormal SeHCAT retention with the expression of symptoms suggestive of malabsorption, this has been demonstrated in only 7 of the 16 patients studied.

Furthermore, this figure depends on the definition adopted for an abnormal bowel habit. In this respect the study illustrates one of the difficulties in the interpretation of the retention test. While it is possible to identify individuals whose results fall outside those of the normal group, it is arguable whether they can be considered to have true bile acid malabsorption in the absence of clinical symptoms.

Six of the patients studied considered their bowel habit inconvenient and 2 of these had been referred to specialist clinics for investigation. The findings in this study suggest that bile acid malabsorption should be considered in any patient presenting with diarrhoea after conduit surgery; SeHCAT offers a convenient method by which such cases can be diagnosed and may avoid protracted investigation.

The wide range of both retention results and the incidence of diarrhoea might well be the result of intestinal adaptation in some subjects. Animal experiments examining the response to intestinal resection have demonstrated increased segmental absorption of bile acid, and such studies suggest that the limited resection required for conduit construction would be well compensated (Perry *et al.*, 1974). While no association was noted between the time of surgery and the result of the retention test, it is impossible without further evidence to be certain that adaptation does not occur. Furthermore, adaptation may occur by mechanisms other than villous hypertrophy, and full characterisation of the changes in bile acid metabolism after conduit surgery will require analysis of faecal bile acid excretion.

It remains doubtful whether bile acid malabsorption after conduit surgery places the patient at risk of oxalate urolithiasis, although the complication is well recognised following jejuno-ileal bypass surgery, with 10% of patients forming oxalate stones (Clayman and Williams, 1979). Normally, dietary oxalate forms insoluble calcium salts which cannot be absorbed in the colon, some 50% of ingested oxalate being excreted in the faeces. Severe bile acid malabsorption reduces jejunal bile concentration, which causes fat malabsorption and calcium saponification; oxalate remains soluble and can be passively absorbed from the colon. The finding of normal urinary oxalate excretion in this study suggests the degree of bile acid malabsorption to be insufficient to induce fat malabsorption and consequent alteration in oxalate absorption.

It was concluded that an abnormal SeHCAT retention test was associated with an alteration in bowel habit in 43% of patients undergoing conduit surgery. It is suggested that bile acid malabsorption should be considered in any conduit patient presenting with alteration of bowel habit who proves to have normal results on routine investigation. The SeHCAT retention test provides a convenient means of making this diagnosis.

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Assessment of the Malignant Potential of Cystoplasty

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Summary—The study group comprised 34 patients with either an ileal augmentation cystoplasty or a colonic substitution cystoplasty. The histological appearance of the intestinal segment, suture line, bladder remnant and bacterial colonisation of the urine and urinary nitrosamine levels were recorded.

There was a high incidence of histological abnormalities, the more significant of which correlated with heavy mixed bacterial growth on urine culture and with high levels of urinary N-nitrosamines. This group of compounds is thought to act as carcinogens in both bladder and bowel under certain circumstances.

It was concluded that patients undergoing lower urinary tract reconstruction using intestinal segments should be considered at risk of developing malignant change either in the intestinal segment or in the bladder remnant. Close long-term follow-up of these patients is essential.

It is recognised that patients with ureterosigmoidostomies are at risk of developing an adenocarcinoma at or adjacent to the ureterosigmoid anastomosis. The increased risk of developing such tumours compared with the normal risk of developing a carcinoma of the colon has been variously estimated at 100-fold (Stewart, 1986), 500-fold (Iannoni *et al.*, 1986) and 7000-fold in young adults (Gittes, 1981). This can be interpreted as a 5% risk of developing a carcinoma for any patient with a ureterosigmoidostomy. This risk has been attributed to the exposure of colonic mucosa to a mixture of urine and faeces (Gittes, 1986) in which Stewart *et al.* (1981) demonstrated the presence of such recognised carcinogens as the N-nitrosamines.

N-nitrosamines are formed when urinary nitrate is reduced by colonic bacteria and reacts with endogenous secondary amines. N-nitroso compounds have also been found in the bladders of patients with Bilharzia and with mixed bacterial infections (Hicks *et al.*, 1982), suggesting that faeces may not be an absolute requirement for their formation and that intestinal segments transposed into the urinary tract may not be free from risk.

We report the initial results of a follow-up study of patients who underwent ileal augmentation cystoplasty and colonic substitution cystoplasty and we attempt to assess the malignant potential of cystoplasty by assessing histological changes, the presence of bacteriuria and the levels of urinary N-nitrosamines.

Patients and Methods

Thirty-four patients were included in the study. Their ages ranged from 9 to 70 years; 15 (Table 1) underwent cystoscopy and cold cup biopsy of their cystoplasties. Biopsies were taken from the intestinal segment, the anastomosis and the bladder remnant. These were stained with haematoxylin and eosin, PAS and High Iron Diamine Alcian Blue (HIDAB) and examined under the light microscope.

Twenty-seven urine samples were collected from 23 patients (Table 2) and assayed for N-nitrosamine content. A 20-ml mid-stream urine sample was obtained; 10 ml were sent for routine microscopy and culture and 10 ml were mixed with 0.5 g

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Read at the 45th Annual Meeting of the British Association of Urological Surgeons in St Helier, June 1989

Table 1 Patients Biopsied

Colonic substitution cystoplasty	8
Ileal augmentation cystoplasty	7

Table 2 Urines Assayed for N-Nitrosamines

	Patients	*Samples*
Colonic substitution cystoplasty	12	13
Ileal augmentation cystoplasty	11	14

sulfamic acid to remove any residual nitrite and thus prevent the artefactual formation of nitrosamines. The samples were snap frozen until the assays could be performed.

Urinary N-nitrosamine levels were measured by the method described by Pignatelli *et al.* (1987) using a British Oxygen Luminox 101A chemiluminescence analyser at the University of Surrey.

Results

In the colonic substitution cystoplasty group (Table 3), all of the "intestinal" biopsies showed inflammation with an infiltrate of lymphocytes or plasma cells and a few eosinophils. The anastomotic biopsies showed an inflammatory infiltrate in all 8 patients and squamous metaplasia in 3. In these 3 the biopsies of the bladder remnant also showed squamous metaplasia and in 1 of these patients there were areas of keratinising squamous metaplasia, a change regarded as pre-malignant by some. In the remaining 5 bladder remnant biopsies, 4 showed inflammatory infiltrate and 1 was normal. All 8 patients had bacteriuria, but the 3 with squamous metaplasia had more than 300 white cell and a heavy mixed growth of bacteria in their urine. (In a separate review of a larger group of patients it was found that 85% of those with colonic substitution cystoplasties had bacteriuria).

Table 3 Colonic Substitution Cystoplasty in 8 Patients

Histology (H and E sections)	*Colon*	*Anastomosis* *Colon*	 *Bladder*	*Bladder*
Chronic inflammation	8	8	4	4
Squamous metaplasia			3	3
(Keratinising squamous metaplasia				1)

The HIDAB preparations from the colonic substitution group revealed some interesting findings. On the colonic side of the anastomosis there were changes in the epithelial mucin distribution consistent with the 'transitional' type of colonic epithelium described by Filipe and Branfoot (1978). This altered pattern of mucin distribution is seen in the colonic epithelium adjacent to colonic tumours and is regarded as a pre-malignant change.

Table 4 Ileal Augmentation Cystoplasty in 7 Patients

Histology (H and E sections)	*Ileum*	*Anastomosis* *Ileum*	 *Bladder*	*Bladder*
Chronic inflammation	7	7	5	3
Villous atrophy	6	7		
Squamous metaplasia			2	

In the ileal augmentation group (Table 4), 6 of 7 'intestinal' biopsies showed villous atrophy. The anastomotic biopsies all showed villous atrophy with inflammatory infiltrate on the ileal side. The urothelium at the anastomosis showed a variety of changes. In 2 there was slight hyperplasia, in 4 there was chronic inflammatory infiltrate, 2 of which also showed squamous metaplasia; in the seventh case the urothelium was flattened with focal goblet cell metaplasia. The bladder remnant biopsies were normal in 3 cases, showed inflammatory infiltrate in 3 and hyperaemia in 1. Only 3 of these 7 patients had bacteriuria but 5 had more than 40 white cells/µl. The remaining 2 had small numbers of white cells in their urine. Of the 2 patients with squamous metaplasia, 1 had a mixed bacterial growth and the other had 80 white cells but no bacteria at the time of investigation. She has had symptomatic urinary tract infections on several occasions since her operation. (In the separate review of a larger group of patients alluded to above, 57% of patients with ileal augmentation cystoplasties had bacteriuria).

All of the urine samples contained N-nitrosamines in quite large amounts (Table 5) similar to the levels found in patients with Bilharzia (Hicks *et al.*, 1982) and considerably higher than the levels found by Stewart (1986) in patients with ureterosigmoidostomy. The higher levels correlated with the presence of a heavy mixed bacterial growth and with the more severe inflammatory and metaplastic changes.

Discussion

The histological investigation showed universal chronic inflammation but no evidence of cellular

Table 5 N-Nitrosamine Content of the Urine

	Mean value (umol/l)	*Range (umol/l)*
Colonic substitution cystoplasty	28.5	3.8–91.6
Ileal augmentation cystoplasty	18.1	7.9–27.1

atypia or dysplasia in the colonic biopsies. It has been suggested that the malignant change occurring in association with ureterosigmoidostomy may be due to chronic inflammation secondary to exposure to urine and it is well recognised that malignant change may develop as a result of chronic inflammation. The inflammation was associated with a mixed bacterial growth in all of these patients. The 'transitional' type epithelial mucin distribution seen in 3 patients at the anastomosis may be an early harbinger of the carcinogen-initiated tumours which might develop in a further 10 to 15 years (these appearances were seen in biopsies from patients who had undergone their surgery 2 to 5 years previously). Add to this the finding of high levels of the carcinogenic N-nitroso compounds in all of the urines assayed and it is hard to believe that this group is not at risk. In fact there may be an increased risk of adenocarcinoma in the colonic segment of the cystoplasty and of squamous carcinoma in the bladder remnant, since both chronic infection and nitrosamine exposure are known to be associated with the bladder tumours in Bilharzia (Hicks *et al.*, 1982) and have been linked with the development of adenocarcinoma in association with ureterosigmoidostomy (Stewart *et al.*, 1981).

The finding of squamous metaplasia at the anastomosis and in the bladder remnant in 3 of the patients in this group and the keratinising squamous metaplasia seen in 1 patient are causes for concern.

It is generallly believed that ileal segments used in the urinary tract do not carry the risk of malignant change. There have been very few reported instances of tumours occurring following ileal conduit diversion (Shousa *et al.*, 1978) and ileocystoplasty (Stone *et al.*, 1985). In this study, 47% of patients with ileal augmentations had bacteriuria and 88% had more than 40 white cells in their urine. All of the tumours reported by Stone *et al.* (1985) developed at the ileovesical anastomosis and chronic infection was cited as an aetiological factor.

In this study the anastomotic biopsies in all 7 patients showed villous atrophy and inflammatory infiltrate on the ileal side with urothelial changes on the bladder remnant side in 6 and squamous metaplasia in 2. The bladder remnant biopsies showed inflammation in 1 and hyperaemia in another. These 2 patients had bacteriuria and again all of the urine samples assayed for N-nitrosamines showed high levels. The significance of the pyuria found in these patients is unclear. It has been recognised that pyuria does not necessarily indicate active infection and presumably in these patients it is more an indication of inflammation in the cystoplasty wall with low levels of bacteriuria.

We feel that all patients who undergo lower urinary tract reconstruction using intestinal segments should be considered at risk of developing malignant change in the intestinal segment or the bladder remnant, particularly when colon is used, because of the high incidence of bacteriuria and its association with high urinary N-nitrosamine levels. These patients should be regularly followed up with cystoscopy and biopsy. Attempts to sterilise the urine using long-term antibiotic prophylaxis may be worthwhile (Mansson *et al.*, 1986). Further studies of the histological changes are required and investigation of the application of more specialised staining techniques is under way.

The relative incidence of malignant change in an intestinal segment used for cystoplasty may reflect the natural incidence of tumour formation in the gastro-intestinal tract. Tumours would be expected to occur more often in the sigmoid colon segments than in caecal and ascending colon segments and for tumours to develop in small bowel segments should be rare. With this in mind, gastrocystoplasty should be viewed with caution because of the high natural incidence of gastric cancer and the identification of nitrosamines as a possible aetiological factor (Hill, 1980).

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Assessment of Volume Measurement of the Prostate Using Per-rectal Ultrasonography

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Summary—A study was made of 100 cadaveric prostates (71 benign glands and 29 invaded by adenocarcinoma) using a technique that enabled per-rectal ultrasonography to be carried out and their volumes measured by computed planimetry. These volumes were compared directly with the actual volumes of the glands measured after dissection from the cadaver specimens.

A high degree of correlation was obtained for the measurement of benign glands ($r = 0.982$) and glands containing cancers confined within the capsule ($r = 0.961$). Estimation of the size of cancers unconfined to the gland was poor and measurement was not possible with 3 malignant prostates that had extended beyond the prostatic capsule so that the ultrasonic boundary could not be defined.

Digital examination is unreliable in determining the size of the prostate gland (Meyhoff and Hald, 1978). As a result, techniques have been developed to measure the volume of the prostate gland by various imaging processes.

The prostatic capsule can be displayed by ultrasound and in recent years per-rectal ultrasonography has become a valuable method of imaging the prostate gland. Watanabe *et al.* (1974) showed that there is good correlation between the volume determined by transrectal ultrasound and the actual volume obtained from specimens removed after "subcapsular prostatectomy". Other groups have demonstrated similar findings (Hastak *et al.*, 1982; Miyazaki *et al.*, 1983).

However, all methods of assessing the accuracy of these volume measurements have been carried out indirectly, *i.e.* with adenomas removed at operation and not with the actual prostatic volumes. A study is described to determine the accuracy of per-rectal ultrasonography in direct comparison to the actual volumes of cadaver prostates.

Materials and Methods

Using a technique of per-rectal ultrasonography of cadaver specimens (Jones *et al.*, 1989), the volumes of 100 cadaver prostates were measured ultrasonically by computed planimetry and compared with their actual volumes measured after dissecting the specimens.

The specimens were scanned in a specially designed perspex tank (Fig. 1). Accurate orientation of the prostates was maintained for standardisation using a vertical catheter in the urethra.

The equipment consisted of a radial probe mounted on an Aloka chair. A Searle Pho/Sonic Alpha Series ultrasound scanner was used together with a multiformat camera with permanent record made on X-ray film.

Results

One hundred cadaver prostates were examined. Three glands were unmeasurable as the margins of the prostate could not be defined. All 3 were unconfined cancers with no clear macroscopic edge to the tumour or ultrasonic boundary. The values

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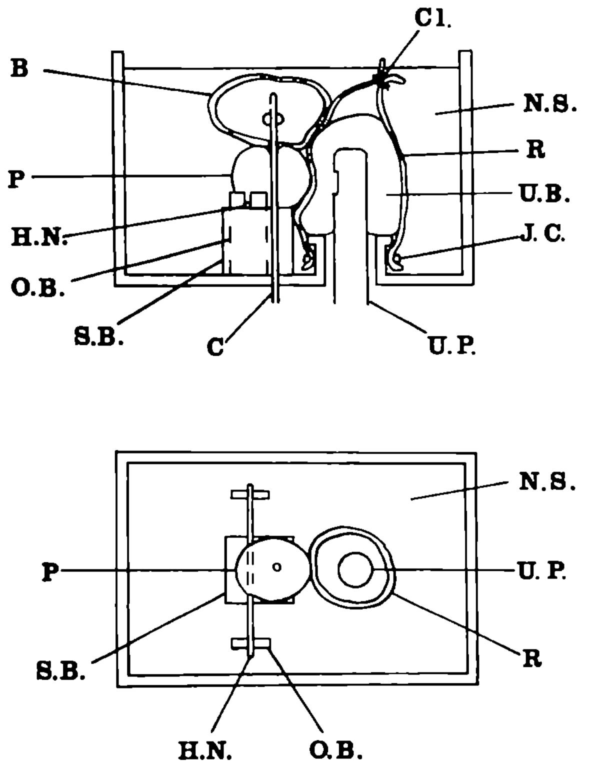

Fig. 1 Scanning tank B = bladder. P = prostate H N = horizontal needle. O.B. = orientation block. S.B. = support block. C = catheter. U.P. = ultrasound probe. J.C. = jubilee clip U B. = ultrasound balloon. R = rectum N S. = normal saline. Cl = clip.

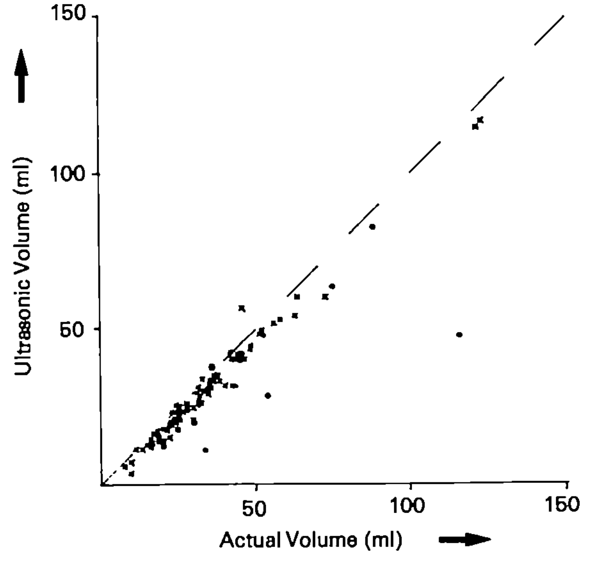

Fig. 2 Comparison of ultrasonic and actual volumes of the prostate. x = benign (r = 0.98). • = malignant (r = 0.85). Mean difference = 4.6 ml.

of the remaining 97 prostates were correlated (Fig. 2). Pathological examination of the 100 prostates showed that 71 were benign and 29 were invaded by adenocarcinoma; 16 cancers were confined within the capsule and 13 were unconfined (Table).

Benign glands

All benign prostates (71) could be measured accurately and a high degree of correlation was present between the actual and ultrasonic volume measurements ($r = 0.982$). The prostates ranged in volume from 10 to 123 ml (mean 32.65). A mean difference of 3.076 ml (standard deviation 3.263) and maximum differences of -13 ml and $+12$ ml were present.

Confined prostatic cancer

The volumes of 16 prostates that contained cancers confined within the capsule were obtained. There was a high degree of correlation ($r = 0.961$) of the actual and ultrasonic volumes. The prostates ranged from 10 to 121 ml (mean 37.9). The mean difference was 5.89 ml (standard deviation 7.15).

Unconfined prostatic cancer

Thirteen prostates contained cancers unconfined by the capsule, 3 of which could not be measured as the ultrasonic boundary was not adequately seen. The correlation of actual and ultrasonic volumes of the remaining 10 glands was 0.799 with a mean difference of 13.1 ml (standard deviation 19.6). In 3 glands the measurements were particularly inaccurate but the remaining 7 were acceptable.

Discussion

This study has demonstrated that the technique of per-rectal ultrasound measurement of the volume of the prostate gland using computed planimetry is accurate in benign glands ($r = 0.98$) and in those containing cancers confined to the capsule ($r = 0.96$). This is because the ultrasonic boundary is intact.

Measurement of prostates containing cancers which were unconfined was sometimes accurate but often inaccurate or impossible to perform ($r = 0.78$ of those measured). This is to be expected as the edge of the gland is often poorly defined or absent ultrasonically and easily misinterpreted on scanning.

The measurement of prostatic volumes can be used to assess the size and progress of the primary tumour. It is also of value for volume measurement in patients with intermediate size benign hypertro-

Table Comparative Accuracy of Volumetric Measurement of the Prostate

Histology	*Total*	*No Measured*	*Correlation (r)*	*Mean difference*	*Standard deviation*
Benign (10–123 ml, mean 32.65)	71	71	0.982	−3.076	3.263
Confined cancer (10–121 ml, mean 37.9)	16	16	0.961	−5.89	7.15
Unconfined cancer (19–116 mls, mean 51.4)	13	10	0.779	−13.1	19.6

phy in order to determine the appropriate operative treatment, since rectal examination can be misleading.

Per-rectal ultrasound volume measurement of the prostate gland is therefore accurate when the capsule is seen and this is useful clinically.

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Treatment of Chronic Prostatitis and Prostatodynia with Pollen Extract

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Summary—Chronic abacterial prostatitis and prostatodynia are notoriously difficult both to diagnose and to treat. These patients tend to have received several courses of antibiotics, anti-inflammatory agents or adrenergic blockade and various other therapeutic manoeuvres with little success. The pollen extract, Cernilton, is reported to be effective in the treatment of this condition and we present the results of an open trial with Cernilton in a group of 15 patients with chronic prostatitis and prostatodynia. In 13 patients there was either complete and lasting relief of symptoms or a marked improvement; 2 patients failed to respond.

Cernilton was found to be effective in the treatment of chronic prostatitis and prostatodynia. Its precise mode of action is not known, although experimental studies suggest that it has anti-inflammatory and anti-androgenic properties.

The treatment of chronic, relapsing non-bacterial prostatitis presents a formidable challenge to the clinician. It is also well recognised that other conditions, such as pelvic floor myalgia, prostatodynia, adductor muscle strain and chronic traumatic osteitis pubis, may give rise to symptoms of dysuria, perineal, groin, testicular and suprapubic pain that mimic inflammatory disease in the prostate (Segura *et al.*, 1979; Osborn *et al.*, 1981; Buck *et al.*, 1982). It is, therefore, important to differentiate such conditions from chronic prostatic inflammation on the basis of objective morphological, biochemical, radiological, urodynamic and microbiological criteria.

To achieve a cure in these patients is extremely difficult. The response to antibiotics, α-adrenergic blockage, non-steroidal anti-inflammatory drugs and other empirical manoeuvres is either ineffective or, at best, variable (Meares and Barbalias, 1983; Meares, 1986). The pollen extract Cernilton (A. B. Cernelle, Sweden) has been used in the treatment of chronic prostatitis for nearly 30 years with favourable results (Ask-Upmark, 1963; Denis, 1966; Ebeling, 1986; Saito, 1967). The aim of this study was to evaluate the efficacy of Cernilton in the treatment of patients with chronic non-bacterial prostatitis and prostatodynia.

Patients and Methods

Fifteen patients, ranging in age from 23 to 63 years (mean 42.9 ± SD11.1) and with a clinical diagnosis of chronic relapsing non-bacterial prostatitis or prostatodynia, were entered into an open trial to study the effect of Cernilton. Twelve patients had previously been treated with 1 or more courses of antibiotics for varying periods of time, 4 had been treated with an alpha-adrenergic blocker, 1 had undergone a transurethral resection of the prostate and 1 an epididymectomy without relief of symptoms. At the time that the patients were commenced on Cernilton they had suffered from their symptoms for periods ranging from 5 months to 7 years (mean 3.3 ± SD2.2). Their clinical presentation was as follows: 13 complained of irritative urinary symptoms, mainly dysuria (13) and frequency (6). All complained of pain or discomfort, either persistent or intermittent, localised to the testis (7), groin (4), perineum (5), suprapubic area (1) urethra/penis (3) or on ejaculation (2) (Table).

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Table Details of Patients

					Previous therapy			
Name	*age (years)*	*Dur. of symptoms (years)*	*Urinary symptoms*	*Pain site/ occurrence*	*Antibiotics*	*Relaxants/ α adrenergic blockade*	*Previous surgery*	*Response to Cernilton*
TW	36	7	Dysuria	L testis	Multiple		Epididymectomy	Complete
DD	61	5	Dysuria	Suprapubic	None	Yes	TURP	Partial
FM	49	0.5	Dysuria	Lumbosacral	None			Partial
GS	47	2	Dysuria	L testis	Multiple			Partial
DB	33	1	Frequency	R testis	Multiple			Complete
JG	46	2	Dysuria, frequency	Perineum, ejaculation	Multiple		Cystoscopy	None
MP	44	7	Dysuria	Groin	Multiple	Yes	Cystoscopy	Complete
RJ	29	1	Dysuria, frequency	Perineum, penis	Multiple		Cystoscopy	Complete
DP	51	4	Dysuria	Perineum, testes	Multiple			Partial
HG	63	2	Frequency	Penile, on intercourse	Single	Yes	Cystoscopy	None
SC*	36	2	Dysuria	L. testis, groin	Multiple			Complete
DH	40	7	Dysuria	Perineum, testes	Multiple			Partial
JM	35	3	Dysuria	Testes, urethra	None	Yes		Partial
RD*	23	3	Dysuria	Groins	Multiple			Complete
AP	51	3	Frequency	Groins, perineum	Multiple	Yes	Cystoscopy	Complete

* Patients SC and RD relapsed when treatment was stopped and responded again to further treatment

The diagnosis of chronic prostatitis or prostatodynia was made on the basis of the segmented urine sample method of Meares and Stamey (1968). No significant bacteriuria was present in any of the patients, nor were pathogenic organisms, including *Chlamydia trachomatis*, cultured from the EPS (expressed prostatic secretion). In 5 patients the pH of the prostatic fluid was alkaline (pH 7.0–8.0) with >10 leucocytes and fat laden macrophages/high power field on microscopy. In 8 patients the characteristics of the EPS were normal (pH <6.5; pus cells <10/HPF) and in 2 cases no fluid could be obtained by massage for examination. The patients were commenced on Cernilton 2 tablets twice daily and assessed clinically at monthly intervals.

Results

The duration of treatment with Cernilton varied from 1 to 18 months. Seven patients became symptom-free, 6 were significantly improved and continue to take Cernilton regularly, and 2 failed to respond. Most patients (11) did not begin to show any improvement in signs or symptoms until 3 months after starting treatment (Table). Only 1 patient, with a 12-month history of right testicular pain and urinary frequency, who had received 3 courses of antibiotics, with sterile urine and an EPS pH of 6.8 with <5 leucocutes/HPF, was completely relieved of symptoms after 1 month's treatment with Cernilton. A second patient with a 5-month history of dysuria, frequency, back ache and sterile urine, but with an EPS pH of 8 and >20 pus cells/HPF, was partially relieved of symptoms at 2 months and the pH of the EPS fell to 7.8, <10 pus cells/HPF.

Two patients had a recurrence of symptoms after cessation of treatment. A 36 year-old man had a 2-year history of intermittent dysuria, left groin and testicular discomfort and an EPS pH of 8 with masses of pus cells/HPF on microscopy; he had been treated with several courses of antibiotics (minocycline, doxycycline, trimethoprim) without relief of symptoms or a change in the alkalinity or leucocytosis of the EPS. After 3 months' treatment with Cernilton the symptoms were completely relieved and the pH of the EPS fell to 7.1 with <5 pus cells/HPF. On discontinuing treatment the symptoms recurred, with a return to leucocytosis and an alkaline shift in the pH of the EPS. After recommencing Cernilton the signs and symptoms again reverted to normal.

Discussion

Cernilton is an extract of various pollens from different plants. The active ingredients are a water-soluble (T60) and fat-soluble (GBX) fraction. The water-soluble fraction attenuated the inflammatory response in experimental animals (Ito *et al.*, 1984). The acetone-soluble fraction was found to consist of 3β-sterols with a similarity on UV absorption spectra to oestrone and stigmasterol (Kvanta, 1968). More recently, *in vitro* studies have shown that GBX inhibits cyclo-oxygenase and lipoxygenase enzyme in the eicosanoid cascade, blocking both leukotriene and prostaglandin synthesis (Loschen, personal communication). Cernilton was shown to reduce significantly the size of the ventral and dorsal prostate in the rat and to inhibit testosterone-induced prostatic hypertrophy in the castrated animal (Ito *et al.*, 1986). Kimura *et al.* (1986) observed that T60 and GBX produced relaxation of the smooth muscle of the mouse and pig urethra and increased the contraction of the bladder muscle.

Although the precise mode of action of Cernilton on the inflammatory process in the prostate is not known, it has been shown to be effective in the treatment of chronic abacterial prostatitis (Ohkoshi *et al.*, 1967; Ebeling, 1986). In this study, Cernilton was found to relieve completely the symptoms of prostatitis in 7/15 patients and a further 6 were markedly improved. All patients had previously received several courses of antibiotics, analgesics and muscle relaxants and some were given adrenergic blockade, without effective or lasting relief of symptoms. It is of interest that the effect of the pollen extract was mainly observed after 3 months or more of treatment. Most patients have opted to continue with treatment and no adverse side effects have been reported. The *in vitro* experiments suggest that it could be either a potent cyclo-oxygenase and lipoxygenase inhibitor or a smooth muscle relaxant. These actions could explain its anti-inflammatory effect in abacterial prostatitis and symptomatic relief in prostatodynia, a condition in which an increase in the maximum urethral closure pressure and spasm of the external sphincter mechanism has been observed in association with a diminished urine flow rate (Buck, 1975; Meares and Barbalias, 1983). Conversely, it may affect metabolic processes within the prostatic cell (Habib, personal communications). Further clinical and laboratory studies are necessary to elucidate the exact mode of action of this compound.

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Acid Phosphatase Levels in Serum during Transurethral Prostatectomy

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Summary—Serum prostatic acid phosphatase (S-PAP), serum electrolytes, blood loss and volume of irrigating fluid absorbed were measured during 10-min periods in the course of 35 transurethral prostatic resections. Elevation of the S-PAP concentration occurred in association with a large blood loss, with absorption of irrigant followed immediately by hyponatraemia, and with a sudden drop in systolic blood pressure. The volume of blood lost during irrigant absorption was the most important index of the S-PAP level. A model for the transfer of PAP to the circulation during TURP is presented.

Transurethral resection of the prostate (TURP) is often accompanied by an increase in the serum prostatic acid phosphatase concentration (Marberger *et al.*, 1957). It has been suggested that S-PAP can be used as a marker for the degree of irrigant absorption (Norlén *et al.*, 1986a, b) and that S-PAP is a more accurate predictor of mental changes that may follow upon resection that the serum sodium level (O'Donnell, 1984). However, the factors influencing S-PAP elevation in the course of TURP have not been investigated. The purpose of the present study was to identify factors associated with the S-PAP level during 40 transurethral prostatic resections, and to examine the validity of these 2 hypotheses concerning the significance of S-PAP elevation during TURP.

Patients and Methods

Forty patients scheduled for TURP because of benign prostatic enlargement (mean age 69 years, SD 6) were studied. Appropriate patient and institutional approval was obtained. Rectal palpation was not performed during 24 h prior to surgery. Epidural anaesthesia was given to all patients. The blood haemogloblin, serum sodium (S-Na) and serum prostatic acid phosphatase concentrations were measured after induction of anaesthesia, every 10 min during TURP and 1 and 2 h post-operatively. S-PAP was analysed by radioimmunoassay (Farmos Diagnostica, Finland) with a coefficient of variation of 3%. The sensitivity of the assay was 0.5 μg/l, at which figure all smaller values were set in the statistical analysis.

During TURP the irrigating fluid used was 2.2% glycine. Post-operatively it was 0.9% saline. Resection was performed using the intermittent bladder-filling technique. The irrigant absorption was measured every 10 min during TURP as the difference between the volumetric fluid balance and the blood loss. Absorption was classified as presumably intra- or extra-vascular according to whether or not it resulted immediately in a significant decrease in the S-Na level (2 mmol/l or more; $P<0.05$) (Hahn *et al.*, 1988). Notes were taken continuously of subjective and objective symptoms during and 2 h after TURP.

Five patients were excluded from the series because of histologically confirmed prostatic cancer (n = 1), erythrocyte transfusions were given (n = 2) and incomplete data (n = 2). Statistical analysis was performed using linear regression analysis and 1-way and 2-way analysis of variance.

Results

The mean weight of the resected prostatic tissue was 25 g (SD 12). Before the operation the S-PAP concentration was at the limit of detection in all

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patients except for 1 who recorded 6.7 µg/l. In 29/35 patients, the S-PAP concentration increased during TURP to a median value of 5.7 µg/l (range 0.6–30). S-PAP elevation occurred in conjunction with the following events. (1) When there was increased blood loss (total >700 ml during resection), the S-PAP level increased gradually, ranging from 2 to 5 µg/l, even if irrigant absorption was small, if any (n = 6). (2) A similar increase usually occurred during irrigating fluid absorption that resulted in an immediate decrease in the S-Na level (n = 7). (3) A sudden drop in systolic blood pressure to 80 mmHg (n = 5) was invariably accompanied by an immediate rise in the S-PAP level ranging from 2 to 7 µg/l. (4) The most pronounced S-PAP elevations, ranging from 7 to 30 µg/l, occurred in patients with the combination of blood loss in excess of 700 ml and irrigating fluid absorption associated with immediate hyponatraemia (n = 7). (Fig. 1). Irrigant absorption with no immediate hyponatraemia did not elevate S-PAP. In 24 of the 29 patients with S-PAP elevation, the highest value was recorded at the end of the operation.

In 6/35 patients the S-PAP concentration during TURP was <0.5 µg/l during all 10-min periods. These resections were uneventful.

When examining all parameters obtained by patient monitoring, the S-PAP level at the end of TURP was most strongly correlated to the blood loss occurring during absorption of irrigant with immediate hyponatraemia ($P < 0.001$) (Fig. 2), less strongly correlated to the total change in the S-Na level ($r = 0.34$; $P < 0.05$) and not significantly correlated to the volume of irrigant absorbed ($P = 0.07$) (Fig. 3). However, a significant influence of low and high irrigant absorption on the S-PAP level for various blood loss volumes was found (Table).

There were no significant differences between the S-PAP level at the end of surgery and 1 and 2 h post-operatively.

No mental symptoms were recorded during TURP. During follow-up, however, a change in mental status occurred in 4 patients. In 1 patient, symptoms consisted of confusion and agitation (S-PAP at the end of TURP 1.8 µg/l) and in the others there was nausea and vomiting (S-PAP 2.6, 10.0 and 30.0 µg/l respectively).

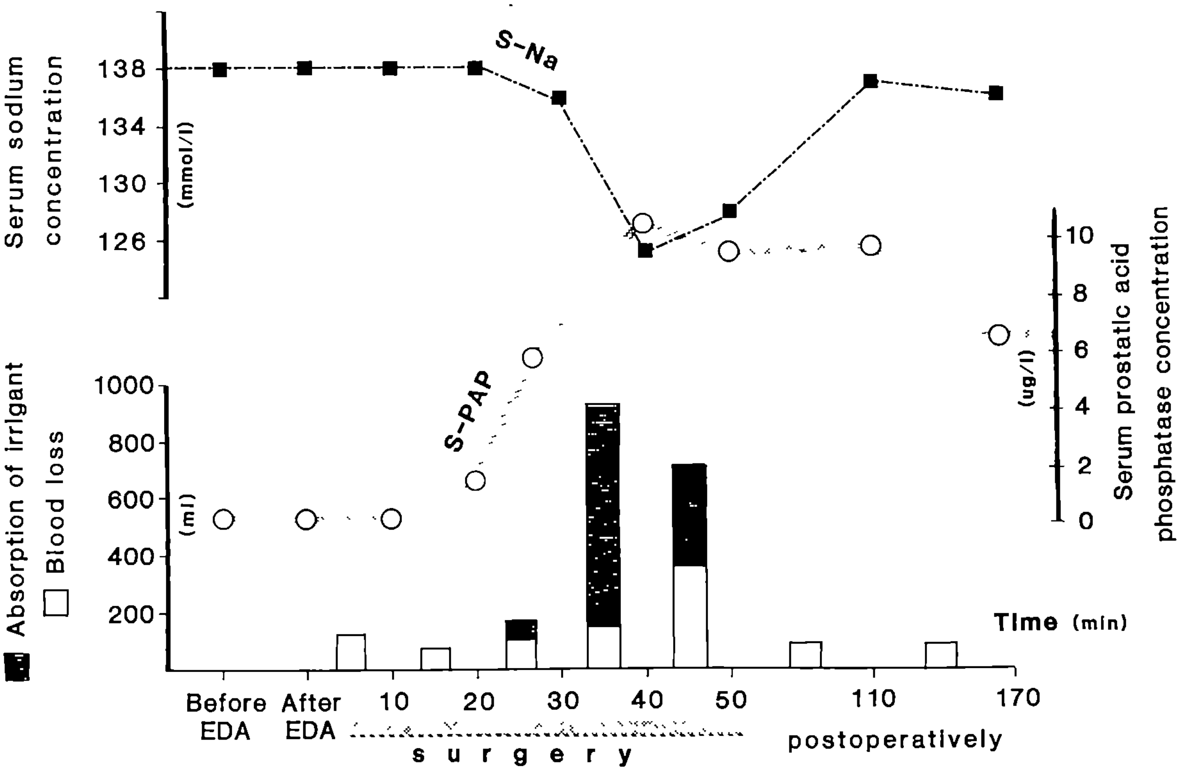

Fig. 1 Serum sodium (S-Na) and prostatic acid phosphatase (S-PAP) concentrations, blood loss and absorption of irrigant recorded volumetrically in one patient with a total irrigating fluid absorption of 1190 ml and a blood loss of 1013 ml during TURP. There were no mental symptoms.

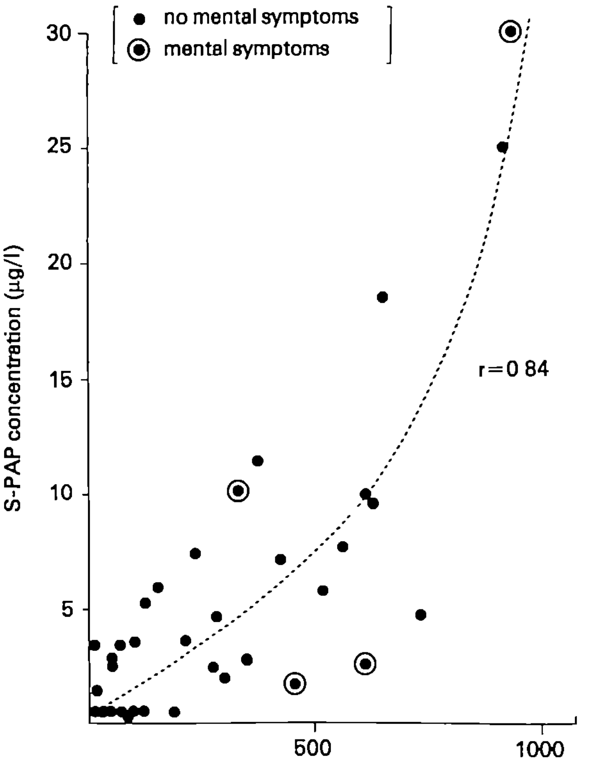

Fig. 2 S-PAP concentration at the end of resection *versus* blood loss during 10-min periods of irrigant absorption associated with immediate hyponatraemia.

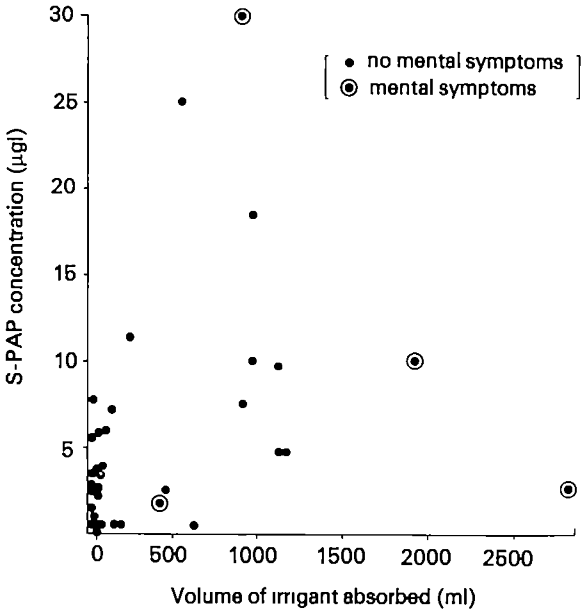

Fig. 3 S-PAP concentration at the end of resection *versus* volume of irrigant absorbed during resection associated with immediate hyponatraemia.

Discussion

PAP is released from the prostatic tissue in the course of TURP and can be readily detected in the irrigating fluid (O'Donnell *et al.*, 1985). In the present study we found an immediate elevation of the serum PAP concentration associated with the absorption of irrigant, which suggests that PAP can be transferred directly to the blood through severed prostatic veins. On the other hand, S-PAP does not seem to be a useful marker for the overall degree of irrigant absorption during TUR (Fig. 3). Neither does this study confirm the hypothesis of O'Donnell (1984) that S-PAP is of importance to the mental symptoms suggestive of a "TURP reaction." Only 4 patients experienced such symptoms, but they had quite variable S-PAP levels. On the other hand, all of them had a substantial

Table Absorption of Irrigant (resulting immediately in hyponatraemia) and Blood Loss during Absorption of Irrigant in Relation to S-PAP Concentration at the End of TUR in 36 patients. (Two-way analysis of variance was used)

				Absorption of irrigant		
				≤300 ml	*>300 ml*	
Blood loss during irrigant absorption	≤300 ml	S-PAP	Median (µg/l)	1.5	3.6	
			Range (µg/l)	0.5–6.0	0.5–7.6	
			n	17	4	
	>300 ml	S-PAP	Median (µg/l)	7.1	10.1	$p<0.001$
			Range	2.9–11.4	2.9–30.0	
			n	5	9	
					$p<0.003$	

Interaction effect $p<0.03$.

absorption of irrigant with immediate hyponatraemia (Fig. 3).

The non-linear dependence of the S-PAP concentration on the volume of irrigant absorbed and the linear correlation to the volume of blood lost during absorption suggest the following model for PAP transfer to the circulation. PAP is not uniformly dispersed in the irrigating fluid, the PAP concentration in the filled bladder probably decreasing with the distance from the operating field; fluid very close to the field would then contain a major portion of the released PAP. This PAP-rich fluid would be the first to enter the blood when irrigant was absorbed into the circulation, and be the chief determinant of the S-PAP concentation. The blood loss during absorption of irrigant probably varies with the calibre of the opened vessels, chiefly veins; major bleeding would indicate a larger area through which the PAP-rich irrigant could enter the circulation.

The increase in S-PAP concentration associated with any sudden drop in systolic blood pressure can probably be ascribed to the dependence of absorption on the pelvic vein pressure (Hultén *et al.*, 1984). This pressure is apt to be lower during arterial hypotension and PAP-rich irrigating fluid can enter the circulation more easily than when the blood pressure is restored.

It is possible that the suggested model for PAP transfer to the blood is also applicable to other prostatic tissue substances, such as prostate specific antigen (Vesey *et al.*, 1988), and for cancer cells that may be demonstrated in the peripheral blood after TURP performed for prostatic carcinoma (Roberts *et al.*, 1962).

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Prostate Specific Antigen—a Screening Test for Prostatic Cancer?

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Summary—A series of 287 patients referred by their family doctors with symptoms of bladder outflow obstruction were asked to attend the hospital for "pre-clinic" screening for carcinoma of prostate (CaP). Blood samples were collected from 211 patients and analysed for serum prostate specific antigen (PSA) and prostatic acid phosphatase (PAP).

Thirty-six patients had a serum PSA > 10 μg/l and 7 had PAP levels > 5 iu/l. In no instance was the PAP elevated without an associated increase in PSA concentration. Patients with raised markers underwent further investigations which included prostatic biopsy and/or resection; 17 patients were proved to have carcinoma of the prostate, 9 of whom had distant metastases. The specificity of PSA for detecting prostate cancer in this study was 90% with a sensitivity of 89.5%, in contrast to values for PAP of 100% and 36.8%.

The routine use of PAP as a marker for prostatic cancer should be abandoned. The use of PSA as a screening test in a group of patients with prostatism appears justified, but with a positive predictive value of only 47%, its use in a mass unselected screening programme is not recommended.

Following the report in 1936 (Gutman *et al.*) showing an increase in phosphatase activity at the site of bony metastases from prostatic cancer, hope was raised of a specific serum marker. Despite the introduction of a radioimmunoassay for PAP, the sensitivity and specificity of the test has not warranted its use as a screening marker for CaP (Gittes, 1983; Vihko *et al.*, 1985).

Prostatic specific antigen, first isolated in 1979 (Wang *et al.*) is a protease produced only by prostatic epithelial cells, normal and malignant. Preliminary evaluation of PSA has shown it to have greater sensitivity than PAP for prostate cancer in localised and metastatic disease (Stamey *et al.*, 1987), but it may be falsely elevated in benign prostatic hypertrophy, prostatic infarction or prostatitis.

The purpose of this prospective study was to evaluate serum PSA as a 'pre-clinic' screening test for CaP in patients who had been referred with symptoms of bladder outflow obstruction.

Patients and Methods

Patients over the age of 50 years with symptoms suggestive of bladder outflow obstruction were identified by scrutinising all family doctor referral letters to one consultant urologist (K.C.V.).

Patients were asked to attend the Pathology Department, where blood was taken and mid-stream urine samples collected. The levels of serum PSA, PAP, creatinine, albumin, alkaline phosphatase and haemoglobin concentration were measured on the blood samples provided.

Serum PSA was measured using the Hybritech Tandem E PSA immunoenzymetric test (Hybritech Europe, Nottingham), reference range < 10 g/l, and PAP as the difference between total enzymic activity and tartrate inhibited activity with a p-nitrophenyl phosphate substrate at 37°C using BCL test kit (Reference range 0–5 iu/l). Patients with raised serum levels of either PSA or PAP were

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recalled for urological assessment. This included cystoscopy and either transurethral resection of the prostate or Tru-cut biopsy. Isotope bone scans were performed on all patients with histologically proved prostatic carcinoma.

Results

A total of 287 patients with symptoms of bladder outflow obstruction were identified from the referral letters. Digital rectal examination of the prostate was either not performed or not recorded in 23% of cases. The diagnosis of CaP was positively suggested in only 8 patients and in only 4 of these was this confirmed histologically.

Of the patients circularised, 26% failed to attend for pre-clinic screening. The reasons for non-attendance are shown in Table 1. Thus 211 patients with a mean age of 68.4 years (range 50–88) were included in the study, of whom 37 with a mean age of 70.2 years (range 58–84) were found to have levels of PSA >10 μg/l. Seven patients had abnormal PAP levels, but all of these had a concomitantly raised PSA >120 μg/l. The 37 patients with abnormal markers were recalled for urological evaluation. Prostatic tissue was obtained by transurethral resection in 29 cases and by Tru-cut biopsy in 7. One patient (PSA 10.6 μg/l) refused to undergo cystoscopy and prostatic biopsy and was excluded from further analysis.

Table 1 Non-attenders

	No
Dead	8
Moved away	4
Symptoms better	3
Too ill to attend	4
Operation done	18
Unknown	39
Total	76 (26%)

Histological examination revealed prostatic carcinoma in 17, benign prostatic hyperplasia in 16, prostatic infarction in 2, with prostatitis in 1 specimen; 30% of patients with normal serum markers subsequently underwent transurethral resection of the prostate and in 2 of these patients histological examination revealed CaP (TO MO).

Benign prostatic disease was found in 73% of patients (19 of 26) with PSA levels between 10 and 30 μg/l. All patients with a PSA >30 μg/l had Ca P. Overall, 53% of patients with a PSA >10 μg/l were found to have benign prostatic disease. (Table 2).

Table 2 Distribution of Patients with Raised Markers

PSA μg/l	*No.*	*CaP*	*M^+*	*Benign (%)*
10–20	21	5	1	76
21–30	5	2	0	60
>30	10	10	8	0
PAP>5 iu/l	7	7	6	0

M = metastases.

Measurement of PAP activities did not confer any additional information, either alone or in combination with the PSA concentrations. Although 6 of the 7 patients with a raised PAP had metastatic disease, 100% of patients (8) with PSA levels >125 μg/l also had metastatic disease.

The sensitivity of PAP (Table 3) as a marker for CaP was 36.8% compared with PSA, which was more than twice as sensitive (89.5%). With a level of 10 μg/l the specificity of PSA was only 90%, but this could be increased to 100% if a level of 30 μg/l was taken as the upper limit of normal; there was, however, a corresponding loss in sensitivity, so that 7 patients with CaP would have been undiagnosed.

Table 3 Sensitivity, Specificity and Predictive Value

	PSA (%)	*PAP (%)*
Sensitivity	89.5	36.8
Specificity	90	100
Positive predictive value	47	100

Patients with prostatic carcinoma had a significantly higher concentration of PSA ($P<0.0001$) and PAP ($P<0.0002$), assuming a one-tailed distribution by the Mann Whitney non-parametric test, than the remaining patients. There was no significant difference in the haemoglobin concentration, albumin, alkaline phosphatase, creatinine or midstream urine samples.

Discussion

Where the demand for urological services exceeds the provision, it is common practice for the priority for consultation to be assessed on the basis of the family doctor's referral letter. The severity of symptoms and the findings of clinical examination are thus important, but rectal examination of the prostate has a low sensitivity in the diagnosis of CaP (≃20%) even in specialist units (Murphy, 1981; Vihko *et al.*, 1985). This renders the assessment of priority unsatisfactory, especially when, in nearly a quarter of our cases, the findings of rectal examination were un-recorded. PAP similarly has a low sensitivity in the diagnosis of CaP, but PSA has not been previously evaluated as a screening marker in patients with symptomatic bladder outflow obstruction.

Only those patients with elevated markers were evaluated, although 30% of those with normal markers subsequently underwent TURP. In 2 of these patients histological examination showed early prostatic cancer (TO MO). The true incidence of CaP in this group, however, remains unknown; 10 μg/l was taken as the upper limit of normal for PSA, because the Hybritech database for PSA suggests that 98% of patients with benign prostatic hypertrophy can be excluded with this level. In this series, however, 76% (16 of 21 patients) with PSA levels between 10 and 20 μg/l had benign histology.

PSA has a sensitivity (89%) for CaP more than double that recorded for PAP (38.9%). This increase in sensitivity was achieved by the diagnosis of patients with non-metastatic disease, which is an important factor in the assessment of a tumour marker.

The specificity of PSA for CaP was high (90%) but although this could be improved by arbitrarily increasing the upper limit, the sensitivity is unfavourably affected.

The usefulness of a test in screening for the presence of disease can also be determined by the positive predictive value (Table 3), *i.e.* the probability that a person with a positive test actually has the disease. In the case of PSA this is estimated to be 47% and for PAP 100%, but all of the patients with an abnormal PAP had grossly elevated PSA levels > 123 μg/l. When this is taken into consideration, the measurement of PAP did not confer any additional value.

Before the advent of PSA, PAP had been the gold standard as a marker for CaP, despite its poor performance. PSA has been shown to be a substantial improvement on PAP in this study, but it has little value in large screening programmes because the sensitivity and specificity will yield a low positive predictive value. However, in a pre-selected group of patients with symptoms of bladder outflow obstruction, its use as a marker appears justified

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Hot Flushes are Induced by Thermogenic Stimuli

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Summary—Hot flushes were caused by hot drinks, alcohol, radiant heaters and thermal blankets in men undergoing treatment for carcinoma of the prostate and in menopausal women. Avoiding or changing these commonplace stimuli appears to reduce the frequency of flushing.

Hot flushes occur naturally in women at the climacteric and are a consequence of falling oestrogen levels. They can also be induced by oophorectomy or anti-oestrogen therapy. Flushes are also reported by men receiving treatment for carcinoma of the prostate. The current therapies for this (orchiectomy, LHRH agonist, oestrogens) aim to reduce testosterone production and 75% of men so treated report flushing as troublesome. These flushes can occur at any time following the start of treatment but, as in women, are most profound when functioning gonads are removed (Erkkola *et al.*, 1973).

The subjective description of a hot flush is variable. It is usually described as a feeling of rising heat in the upper body accompanied by a sensation of general heating with visible reddening of the face and neck (the flush), along with profuse sweating and palpitations (Casper and Yen, 1985). All or some of these symptoms may occur in an affected individual. These flushing episodes can also occur at night, causing regular arousal from sleep, and lead to sleep deprivation and disorder.

Patients and Methods

Amongst the 47 men we regularly reviewed who were being treated for carcinoma of the prostate, hot flushes were considered to be the most difficult side effect. The men complained that specific activities seemed to precipitate an episode of flushing. The increased frequency was most noticed in hot weather, after entering a warm room, after retiring to bed and covering with blankets, during the middle of the night, after meals, after drinking hot tea or coffee, after drinking alcohol, during intense arm activity, such as planing wood, and after cigarettes. Since the first of these factors had previously been associated with a significant increase in hot flushes (Coope *et al.*, 1978), we tested some of the other stimuli to determine cause and effect relationships. The commonplace and repetitive nature of these factors seemed a possible reason for their not having been previously investigated.

Seventeen volunteers were studied. They included 10 men under treatment for carcinoma of the prostate for at least 3 months with either orchiectomy or the LHRH agonist Zoladex. Their average age was 69 years (range 63–78) and they reported an average of 1.6 flushes per day (range 1–4).

Also included in the study group were 4 women suffering from naturally or surgically induced hot flushes. Their average age was 51 years (range 46–57) and they experienced an average of 4 flushes per day (range <1–6). Three female controls were studied. None had suffered hot flushes and all were aged 45.

Subjects wearing normal clothing were seated in a reclining armchair in an air conditioned room controlled between 20 and 22°C. The subject in the adjacent test room was connected to a DEVISES 8-channel recorder via monitors as listed (Fig.). After connecting the leads the subjects were told to rest for 20 min. The following stimuli were then presented in sequence: radiant heating, foil wrap, tea or coffee, whisky, then 10 minutes' resting (Table 1).

The subjects were asked to consume the hot drink and the whisky as quickly as possible,

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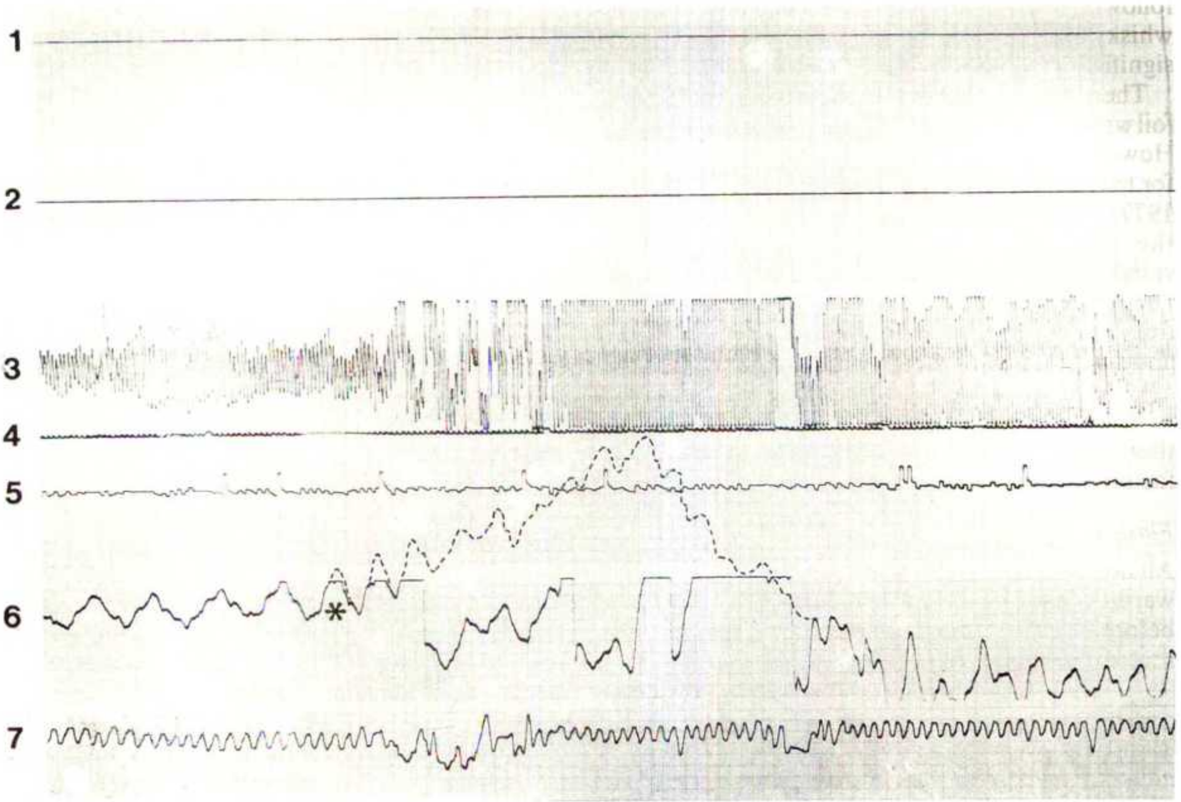

Fig. Polygraph (duration 3 min) showing 7 recording traces before and during a flush. (1) Finger temperature 31.4°C. (2) Groin temperature 35.8°C. (3) Photoplethysmograph. (4) Time. (5) 2-lead ECG. (6) Skin conductance level. Baseline 22.1 → 22.7; the broken line shows the approximate uncorrected change in skin conductance with the flush peaking at 25.7. (7) Respiratory rate. *Hot flush reported.

recording starting as the investigator left the room. They remained alone in the test room, communicating by an intercom, and were asked to report the flush as soon as it was experienced.

Results

Twenty-seven subjective flushes were reported and recorded. (One of these was following a cigarette, which the subject reported as a potent stimulus, and is not included in this report.) For characteristics of flushes see Table 2.

No flushes were observed in the observation period before or after testing, which totalled 30 min per subject.

Comparison of the initial observation period to the stimulus period, using a binomial test, showed that the probability of flushes occurring by chance

Table 1 Stimuli

a. Resting and calibration.
b. Radiant heating, SOLUX 500 radiant heater 1 m from the face on setting 6.
c. Foil wrap, in a life emergency blanket, with only the face exposed. This blanket provides 95% radiant heat reflectance.
d. 250 ml hot tea or coffee.
e. 45 ml of whisky (40% proof).
f. Resting for 10 min before removing the leads.

Table 2 Characteristics of Hot Flushes (Males 16 flushes, Females 10 flushes, Controls nil)

Stimulus	*No. of flushes*	*Average time from starting stimulus (min)*	*Average duration of flushing (min)*
Radiant heat	2	12.5	2.0
Foil wrap	3	8.3	1.4
Tea or coffee	11	10.5	1.5
Whisky	10	11.5	1.3

following the tea or coffee was 0.016 and after the whisky 0.032. This indicated that these factors were significant to the subsequent flush.

There were insufficient flushes in the heating and foil wrap phases to allow this method of comparison. However, by using maximum likelihood estimates for truncated normally distributed data (Wolynetz, 1979), calculations were made. These showed that the time from stimulus to flush lay outside 2 standard errors of the group mean for both radiant heat and foil wrapping. For radiant heat the mean time to a flush was 52 min (−2SE. 40; +2SE. 63) and for foil wrapping 35 min (−2SE. 27; +2SE. 42). This implied that the probability of the flushes occurring by chance was less than 5% and that these stimuli were also significant as precipitating factors.

Flushing

All hot flushes, *i.e.* the subjective feeling of a rising warmth, were reported to occur about 15 to 20 s before or at the start of objective change in the recording parameters.

Vascular

Photoplethysmography gave the most consistent indication of a flush by changes in vascular response (Fig., trace 3). All subjects showed this response with flushes to varying degrees. It was not possible to quantify this response.

Skin conductance level

This showed an abnormal pattern in all flushing subjects (Fig., trace 6). The abnormality was an exaggeration of the sine-wave character. This showed cyclical changes from 8 to 16 cycles/min. Shortly after a flush was reported there was a marked and rapid rise in the SCL value (Fig., broken line) in those who complained of usually sweating with the flushes. A sustained rise >10% of the baseline value accompanied each flush.

Temperature

No marked changes were seen in any of the temperature leads. There was a consistent steady rise in groin temperature (average 0.4°C) during the heating and foil wrap phase, in line with the rise in room temperature (average 2°C). Finger temperature also showed a passive following of the ambient room temperature.

ECG and respiration

Changes were observed in both of these records in some subjects. No particular relationship was found between these parameters and flushes, except that there was generally an increased rate in both parameters after the flush.

Discussion

The probability that the flushes were random events was low, indicating that these simple thermogenic stimuli did induce flushes. Since no differences were observed between the sexes, either in the pattern of responses to stimuli or in the flushing responses themselves, it would appear that the same process was responsible in both sexes.

Our findings for the specific parameters were generally in accord with those of previous workers. The SCL was the best objective indicator of flushes (Tataryn *et al.*, 1980). The unusual fluctuating sine-wave nature to the SCL (Fig.) has been reported by Bini *et al.* (1982) in normal subjects exposed to high temperature. One female subject came back for retest while under hormone replacement therapy and this trace abnormality was then absent. Photoplethysmography also gave good objective results similar to those of other workers, although our recordings were taken from the forehead.

The lack of change in peripheral and groin temperature was in contrast to the findings of Casper and Yen (1985). Their studies were concerned that the changes in temperature were due to local cooling effects, the first records having been taken on naked subjects. However, all of our subjects were fully clothed and the room temperature was relatively cool. It may be a more representative site to measure core temperature in the groin due to the mass of surrounding muscle and the relative lack of sweating at this site. (We specifically did not use internal thermistors, as all of our subjects were volunteers).

The common feature of the test stimuli was that all had an effect on body heat or perception of heat, *e.g.* hot tea and coffee specifically warmed the posterior nasopharanx and induced reflex sweating. This is used in warm climates to increase sweating, the end result being a sensation of cooling. Alcohol produces a feeling of increased gut-warmth and then leads to increased loss of heat by peripheral vasodilation and for this reason is no longer used in hypothermic resuscitation.

Radiant heating eventually increases body heat, as does the foil wrap, by preventing radiant losses. Both are slow to effect a change in body temperature and this is reflected in the relatively fewer flushes after these stimuli.

Those stimuli which subjects associated with flushes, but which we did not test, also have physical features to suggest a similar mechanism. Upper arm activity is mechanically inefficient, producing more heat than work, and this is used during intense shivering, when rapid arm movement is involuntary. Meals are known to contain an amount of heat above the calorific content (specific dynamic action) which is released after ingestion, leading to increased body temperature. Nocturnal flushes may also be explained by a body temperature phenomenon. The peak incidence of these was reported to occur between 0200 and 0300 hours. This happens to be the time at which the diurnal body temperature is at a minimum, followed by a relatively rapid rise (Houdas and Ring, 1982).

From these and other observations (Tataryn *et al.*, 1980) it would appear that the hot flush is a response to thermogenic insult on body temperature control mechanisms, which then respond in an appropriate, albeit exaggerated manner, to maintain body temperature. Using this as a model, the spectrum of hot flush symptoms can be explained, depending on which heat loss pathway is most activated and on the natural variations between individuals. These findings help to explain the increased incidence of hot flushes noticed in warmer seasons (Coope *et al.*, 1978), and the reduced rate in cold conditions (Casper and Yen, 1985).

We attempted to apply some of these findings clinically and found that in men who reduced the temperature of their hot drinks and their night clothing, the frequency of flushing was halved. We also noticed that most of the men attending the clinic had stopped smoking because of its specific association with hot flushes. Questioning of climacteric women revealed that many had also established an association between all of the stimuli and hot flushes, but tended to downplay the significance of them due to their commonplace nature.

It was concluded that hot flushes are induced by thermogenic stimuli. They are an exaggerated physiological response of normal heat loss mechanisms. This finding is of importance to the research into, and the treatment of, hot flushes.

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Early Post-operative Morbidity of Total Prostatectomy

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Summary—Complications were analysed in a contemporary series of 100 total prostatectomies performed, for carcinoma of the prostate, under the supervision of one surgeon. There were 7 major complications including 1 death. No patient had a rectal injury. Minor complications occurred in 33 patients. Severe stress incontinence persisted in only 2 patients and 12 had minor stress incontinence. Of 38 patients potent before surgery and in whom it was possible to preserve both "neurovascular bundles of Walsh", 45% retained post-operative potency. Preservation of potency was related to the pathological extent of the tumour.

It was concluded that in selected patients, total retropubic prostatectomy can be performed safely with good quality of post-operative life.

The management of clinically localised carcinoma of the prostate remains controversial. Different authors advocate conservative management with instigation of active treatment only on evidence of disease progression (George, 1988), radiotherapy by external beam (Bagshaw, 1984) and/or interstitial methods (Whitmore, 1980), hormonal therapy (Barnes and Ninan, 1972) and surgical removal of the entire prostate (Walsh and Jewett, 1980; Paulson *et al.*, 1982; Benson *et al.*, 1984). Differences in selection of patients and methods of reporting progression and survival make comparison of the reported results difficult. The quality of life after primary treatment is of prime importance to the patient and therefore should influence choice of therapy. From a pragmatic point of view, total prostatectomy seems the best method of securing local control but it can interfere with the quality of life by damaging the mechanisms of continence and penile erection. These and other potential complications, such as injury to the rectum and anastomotic strictures, have given the operation a bad reputation in the UK. Recently, modified surgical techniques have reduced the incidence of anastomotic stricture, improved continence post-operatively and preserved sexual function in a subpopulation of patients (Walsh, 1986). The effect of these modifications on the quality of local control has yet to be fully assessed but they have resulted in a new wave of enthusiasm for the operation. The aim of this study was to carry out a critical analysis of the early morbidity of contemporary total prostatectomy.

Patients and Methods

The patients were all referred to the senior author (JBD) at UCLA and all had cytological (fine needle aspiration) or histological confirmation of the diagnosis of malignancy. Metastatic screening, including bone scan, had proved negative and the patients chose surgery after discussion and explanation of the alternative methods of treatment. The operations were performed between 1981 and 1987. The age range of the patients is shown in Figure 1 and their presenting symptoms in Table 1. Those with no urological symptoms had palpable disease diagnosed by routine rectal examination or during investigation for other conditions. In 17 patients the tumour was diagnosed by transurethral resection for apparently benign disease (clinical stage A2 or T0b). Three patients had palpable progression and biopsies showing viable tumour after previous radical radiotherapy. The clinical stage at presentation is shown in Figure 2.

Read at the 44th Annual Meeting of the British Association of Urological Surgeons in Buxton, June 1988

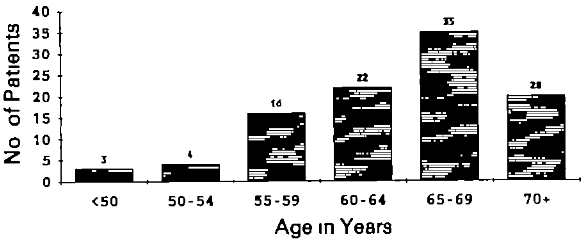

Fig. 1 Age at presentation.

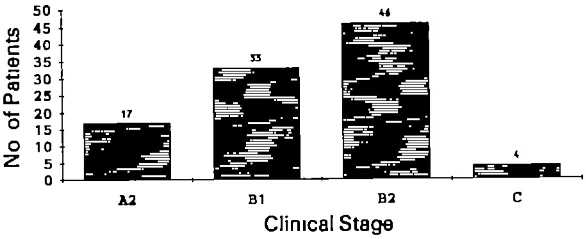

Fig. 2 Clinical stage at presentation.

Surgical Technique

One patient had a perineal prostatectomy and in the others the operation was performed by the extraperitoneal retropubic approach. Pelvic lymph node dissection was performed routinely before the prostatectomy. The dissection was confined to the nodes around the obturator nerve plus any other suspicious-looking nodes. The "nerve-sparing modification" (Walsh and Mostwin, 1984) was introduced during this series. Before 1 January 1985, 7 patients had this modified dissection. After this date, 41 patients (67%) were deemed suitable. The aim of the operation was to remove the tumour completely. Both neurovascular bundles were considered to have been preserved in 38 patients. Suspicion of extraprostatic tumour extension meant that in 10 patients the neurovascular bundle was preserved on one side only. The technique for removal of the gland was essentially that described by Walsh (1986) except that the urethra was not fully divided before 2 lateral and 1 anterior sutures were placed in the urethra distal to the point of transection. Where possible the bladder neck was preserved. Suspicion of tumour at the proximal margin was checked by frozen section histology with wider resection being performed if necessary. If a TURP had been performed, the ureters were catheterised to assist with their identification during reconstruction of the bladder neck. In the latter part of the series the mucosa of the bladder was everted prior to performing the vesicourethral anastomosis. Two Penrose drains were left adjacent to the anastomosis and gradually withdrawn as the amount of drainage diminished. A 22F 2-way urethral Foley catheter was strapped to the penis.

Table 1 Presenting Symptoms

Symptoms	*No.*
None	45
Outflow obstruction	22
TURP	17
Irritative voiding symptoms	3
Post DXT	3
Haematuria	2
"Prostatitis"	2
Rectal bleeding	2
Epididymitis	1
Back pain	1
Impotence	1
UTI	1
Total	100

As a routine, the patient remained in hospital for 1 week and returned to the clinic for catheter removal 2 weeks from the time of the operation.

Follow-up

Data on the post-operative course were recorded prospectively in personal case records. Further information on post-operative continence and sexual function was obtained from personal interview at follow-up visits and by telephone contact. Patients were followed up for an average of 18 months (range 1–65).

Complications

Complications were classified as major or minor. Major complications were those that threatened the life of the patient or required early re-operation. Continence and potency were considered separately.

Results

Major complications occurring in 7 patients are shown in Table 2. The patient who died was an obese man who experienced sudden collapse on the second post-operative day. The clinical differential diagnosis was massive pulmonary embolus versus myocardial infarction. Post mortem was refused by the relatives. The other complications were regarded as major either because they were life-threatening or involved re-operation (3 patients). Catheter displacement in the 48 h immediately after surgery involved re-operation for 2 patients.

Table 2 Major Complications

Complications	*No*
Death	1
Haemorrhage	1
Pulmonary embolus	1
Myocardial infarction	1
GI haemorrhage	1
Displaced catheter	2
Rectal injury	0
Total	7

Minor complications not related to continence or potency are listed in Table 3. These complications are described as minor because they were not life-threatening and were largely self-limiting. Of the 9 anastomotic strictures, 6 required only 1 dilatation. Of the 3 patients who developed lymphoceles, 1 required needle aspiration under ultrasound guidance. The adductor pain and weakness was always self-limiting and was presumably related to obturator neuropraxia occurring during the lymph node dissection.

No association between age, clinical stage or previous transurethral prostatectomy and the incidence of complications was noted.

Pathological Stage

Histology revealed adenocarcinoma in all of the specimens. The pathological staging was B1 in 19, B2 in 42, C (microscopic evidence of tumour involvement and/or penetration of the prostatic capsule) in 26 and D1 (evidence of lymph node metastases) in 13. There was no relationship between the pathological stage and post-operative major or minor morbidity. Two patients with persisting stress incontinence (*vide infra*) had pathological stage B1 and B2 tumours respectively.

Table 3 Minor Complications in 33 Patients

	No
Specific	
Anastomotic stricture	9
Adductor pain/weakness	5
Distal urethral stricture	2
Lymphocele	3
Severe bladder spasms	3
Hydrocele	2
Testicular pain	2
Anastomotic leak	1
Osteitis pubis	1
Penile oedema	1
UTI	1
Inguinal hernia	1
General	
Ileus	1
Chest infection	1
Bronchospasm	1
Delayed wound healing	1
Wound haematoma	1
DVT	1
Cholecystitis	1

Post-operative Continence

Results of return of post-operative continence are shown in Figure 3; 27 patients had complete continence and 58 described occasional leakage of a few drops or urine when tired or under conditions of severe physical stress (VMS). Such patients did not use protective padding or external continence devices. Of these 85 patients with complete continence or very minor stress incontinence, the time taken to reach this status varied from 1 to 80 weeks after removal of the catheter (mean 12.7 weeks). Twelve patients had minor stress incontinence requiring 1 pad or less per day. Two patients had severe stress incontinence and have proceeded to surgery with artificial sphincter implantation.

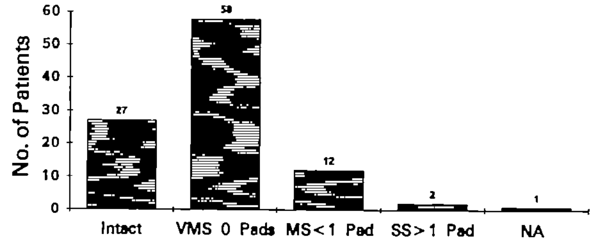

Fig. 3 Post-operative continence VMS = very minor stress incontinence MS = minor stress incontinence requiring 1 pad or less per day SS = severe stress incontinence requiring > 1 pad per day. NA = not assessible

Post-operative Sexual Function

Table 4a depicts the number of patients who were potent, *i.e.* they described the ability to obtain erections suitable for intercourse, those who had partial erections and those were impotent after surgery, and relates this to the procedure performed. Patients who were potent after surgery were younger (mean age 59.2 years ± 8.5 (SD)) than those who failed to regain potency (mean 64.7 ± 5.7) but this difference was not statistically significant. Table 4b relates potency to the pathological stage and shows that the proportion retaining full potency declined with increasing extent of tumour.

Table 4a Post-operative Potency Related to Surgical Assessment of Nerve Preservation

	No.	*Potent*	*Partial erections*	*Impotent*	*Not known*
Nerve preservation					
Both sides	38	17	13	8	–
One side	10	1	6	3	–
Not attempted	50	1	6	41	1
Not known	2	—	—	—	2

Table 4b Post-operative Potency Related to Pathological Stage

Pathological stage	*No*	*Potent*	*%*
B1	19	6	32
B2	42	10	24
C	26	3	12
D1	13	0	0

Table 5 compares the complication rate of this series with that of 1480 patients from previous series.

Discussion

A recent survey of trends in patterns of care for prostatic cancer in the USA has shown that localised cancer now accounts for over half of all cases being diagnosed and that survival has improved for all stages (Schmidt *et al.*, 1986). Whilst there are no corresponding data for patients in this country, such reports indicate that the proportion of cases diagnosed when the disease is still confined to the prostate can be increased. The natural history of such early disease has been said to be capricious but a recent report from this country showed that 84% of apparently localised tumours will progress without treatment (George, 1988). Furthermore, there is evidence that prostatic tumours dedifferentiate with time (Brawn, 1983; Cumming *et al.*, 1989) and that the development of metastases is related to tumour size and differentiation (McNeal *et al.*, 1986).

In order to advocate an aggressive approach to localised disease there has to be an effective treatment, the patient has to have a life expectancy to benefit from any improved survival conferred by the operation, and the morbidity must be acceptable. A return to normal survival after surgery for organ-confined disease has been reported (Elder *et al.*, 1982; Benson *et al.*, 1984).

The results of this study indicate that post-operative morbidity, particularly in relation to post-operative continence, is low. The major complications are those that could be anticipated after any major pelvic operation, although it is distressing to report a death.

The results indicate that continence may take over a year to recover. Reasons for this slow recovery in some patients may include increased bladder compliance, demonstrated in a urodynamic evaluation of incontinence after prostatectomy (Leach *et al.*, 1987). The practical implication of this finding is that intervention for incontinence should not be recommended too early in the post-operative period and should only follow a full urodynamic evaluation.

The results of the nerve-sparing technique are similar to those reported by Catalona and Dresner (1985) but do not reach the 70% reported by Eggleston and Walsh (1985). We were unimpressed by the results of potency from preservation of only one neurovascular bundle, although the number of patients is small. The results of post-operative potency, in common with other published results, do not represent an objective, scientific assessment of erectile function but have been based on patient satisfaction. Our results suggest that the more extensive the tumour, the smaller the chance of

Table 5 Comparison with Published Series

	Mortality (%)	*Rectal injury (%)*	*Anastomotic stricture (%)*	*Incontinence*	
				Severe stress (%)	*Mild stress (%)*
Range (n=1480*)	0–4.8	0–7	2.3–21	1–12.5	5–27.4
Present series (n=100)	1	0	9	2	12

*Based on data presented by Igel *et al* (1987).

successful outcome in terms of preservation of sexual function.

Although evidence has been presented that patients having positive margins were never positive only in the area of the apical dissection used to spare the neurovascular bundles (Eggleston and Walsh, 1985), long-term follow-up of the influence of the nerve-sparing technique on local recurrence is not yet available. Belt and Schroeder (1972) showed that the local recurrence rate after total prostatectomy was 6% if the disease was organ-confined but rose to 22% if the patient had positive margins.

Better staging methods to assist with patient selection for radical therapy represent a continuing challenge. Computed tomography and magnetic resonance imaging, used in assessing some of the patients in this study, were disappointing in this respect (Mukamel *et al.*, 1986), but transrectal ultrasound appears better than digital rectal examination (Andriole *et al.*, 1988).

The morbidity following total prostatectomy has to be compared with that following alternative radical therapy. Complications of external beam radiotherapy are not mentioned in many reports of this treatment but prolonged proctitis has been reported in 61% of one series in which side effects were documented prospectively (Ritchie *et al.*, 1985).

Complications of surgery are usually treatable. The 2 patients who had severe stress incontinence have been rehabilitated with AMS sphincter insertion, and a number of the patients who were impotent have had penile prostheses inserted.

Overall, our results suggest that total prostatectomy can be safely performed in selected patients, with preservation of good quality of post-operative life.

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Fertility after Orchiopexy for Cryptorchidism: a New Approach to Assessment

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Summary—Fifty-six patients treated surgically for cryptorchidism between 1950 and 1975 were assessed for fertility. Their age at the birth of their first child was used as the parameter. A direct comparision with the normal population of different regions was available from the General Register Office of Scotland, obviating the need to use female statistics for comparison. The results showed that only very late surgical treatment of unilateral cryptorchidism affected fertility.

In the absence of statistics on male fertility after orchiopexy, various indirect measurements, including sperm count, hormonal assessment and testicular biopsy, have been used for assessment. Only a limited number of patients have been studied, however, because many fertile patients refused to undergo unnecessary investigations. It is also difficult to correlate these indirect measurements with true fertility in men, unless a method is devised to establish the latter directly. In the present study, a method was used whereby male fertility could be estimated by using statistics available from the General Register Office of Scotland. This can be accurately reproduced, since separate normal values for men and women are available for different regions. It is especially applicable when studying subfertility in a particular group of patients.

Patients and Methods

Questionnaires were sent to 192 patients who received surgery for undescended testes in Peel Hospital, Galashiels, between 1950 and 1975. The operations were mostly carried out by 2 surgeons, using the Keetley–Torek method of orchiopexy.

Questionnaires were sent in sealed envelopes marked "Confidential". Initially, more than two-thirds were returned unopened. However, 7 patients were subsequently traced. For the remainder, General Practitioners were able either to supply patients' addresses or relevant details from their own records.

We were able to contact 113 patients. One was traced on readmission to hospital with a teratoma of the left testis; he had received a bilateral orchiopexy 15 years previously. This was the only instance of malignant change in this study. It was assumed that any children mentioned in the answers to the questionnaire were the patients' own offspring.

The patients were then divided into 4 groups according to the age at which the operation was carried out. They were also subdivided into unilateral or bilateral procedures. Group A patients received surgery when less than 6 years of age, Group B between 7 and 12 years, Group C between 13 and 18 years and Group D when aged over 18 years.

The following information was obtained from the Vital Statistics Department of the General Register Office of Scotland:

1. Table of legitimate live births by sex and age of parents (Regional Health Boards in Scotland for 1985 and 1986) (Fig. 1). Figure 2 shows the same data for women. Both show a rapidly rising peak to 25–29 years followed by a rapid decline.
2. Legitimate live births by sex, number of previous legitimate children (live or stillborn) and duration of marriage, for Scotland. These data were

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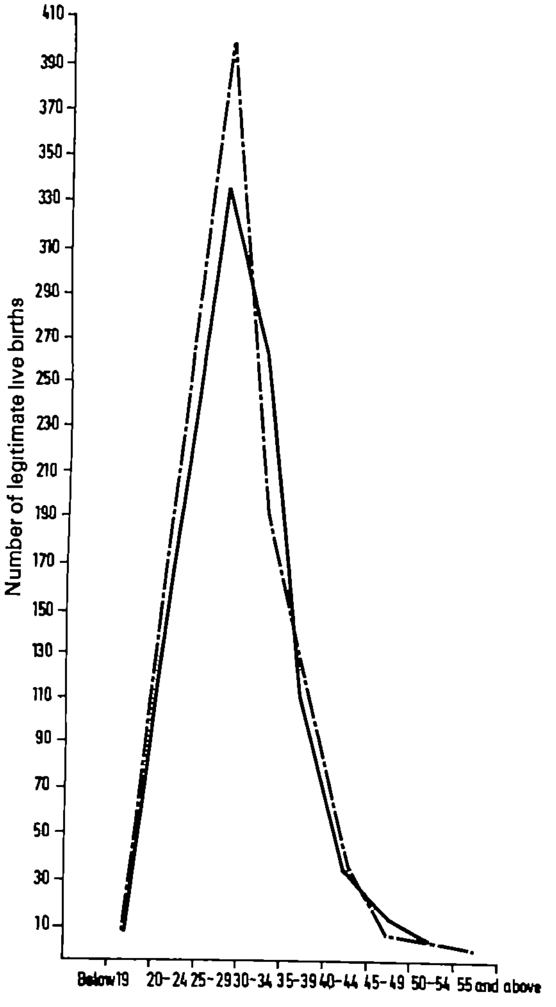

Fig. 1 Number of legitimate live births in Borders regions according to age of father. Dotted line represents 1985. Continuous line represents 1986.

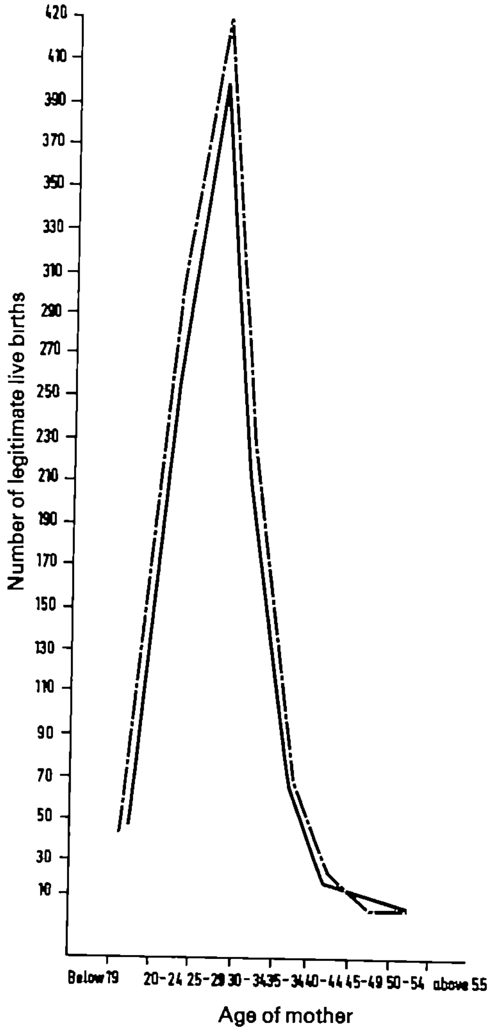

Fig. 2 Number of legitimate live births in Borders region according to age of mother. Dotted line represents 1985. Continuous line represents 1986.

available for the mother only but the pattern of first childbirth according to the mother's age followed the same pattern as above and showed that approximately 75% of women produced their first child within 3 years of marriage.

We then calculated the average age of our patients at the time of their first paternity. This calculation was performed separately for Groups A, B, C and D. We also calculated the percentage paternity by subtracting the percentage of patients with children from the total number of married patients.

Results

Of 113 patients, 71 were married and 42 were unmarried; 56 of these were married with children and their distribution according to age at operation is shown in Table 1.

The 2 proven cases of male infertility had both received bilateral orchiopexy. Of the 3 remaining "infertile" couples, 2 husbands replied that they were unable to have children because of their wife's infertility. However, on examining the records, it was found that in 1 case, where the husband was in the bilateral D group, he had never been tested and

Table 1 Distribution according to age at operation

Group	Age at operation (years)	Married, do not want children	Married with children	Husband infertile (proven)	?Husband ?wife infertile
A	<6	—	1	—	—
B	7–12	5	27	—	—
C	13–18	4	18	1	2
D	>18	1	10	1	1

his wife's gynaecology report showed that probably no intercourse had taken place, as the vagina was very narrow. The second patient was in the unilateral C group and had been operated on twice for variococele, which had developed subsequent to orchiopexy, and he was receiving testosterone to improve the sperm count. The third patient, who had been "trying" for more than 1 year, was found to have a normal sperm count and both he and his wife were attending the fertility clinic.

Table 2 shows the distribution according to unilateral or bilteral operation. Table 3 shows the percentage paternity, calculated from the proportion of married couples with children, irrespective of the duration of marriage. Groups A and B, and groups C and D, were combined as the numbers were small. The overall fertility rate for unilateral cases was 83.9%, for bilateral cases 60% and for all cases 78.9%.

Table 4 shows the age of first paternity for the various groups. Table 4 was plotted (Fig. 3) to compare with the normal individuals in Figures 1 and 2. Group A had only 1 patient with first paternity at 33 years and was not plotted. Bilateral cases were also excluded because of small numbers. Figure 3 shows a sharp contrast between Groups B and C, which are probably normal, and Group D. This group showed delayed paternity when compared with the other groups.

Table 2 Distribution according to Unilateral or Bilateral Operation

Group	Unilateral		Bilateral	
	Married with children	Married without children	Married with children	Married without children
A	1	—	—	—
B	21	2	6	3
C	15	6	3	1
D	10	1	0	2

Table 3 Percentage Paternity

Group	Unilateral	Bilateral
A+B	91 7% (22/24)	66.7% (6/9)
C+D	78 1% (25/32)	50.0% (3/6)

Finally, the average age at paternity was calculated for each group. For unilateral cases this was 26.4 years for Group B, 26.4 for Group C and 30.4 for Group D. For the bilateral cases it was 23.5 years for Group B and 26.6 for Group C.

We abandoned an attempt to correlate the age at first paternity to the age of marriage because many of our patients were fathers either before or immediately after their marriage.

The results are summarised as follow:

1. Bilateral cases showed very poor fertility when operated on after puberty.
2. Unilateral cases showed no change in fertility when compared with the average, unless they were operated on after 18 years of age, in which case there was evidence of subfertility. This finding contradicts that of Lipshultz (1976), who found definite impairment in fertility after unilateral orchiopexy, and of Atkinson (1975), who found no impairment of fertility. However, both of these studies failed to classify their patients and results according to age at operation.
3. There were insufficient cases in Groups A and B to assess accurately any difference in fertility in unilateral or bilateral cases operated on before puberty.

Discussion

Various methods have been used to assess fertility in patients with undescended testes. These include semen analysis (MacCollum, 1935; Hansen, 1949), light microscopy (Charny and Wolgin, 1956; Charny, 1960), hormonal assay (Atkinson *et al.*, 1975), paternity (Atkinson, 1975; Puri and Nixon, 1977) and external morphology (Laron and Zilka, 1969; Puri and Nixon, 1977). Hargreave *et al.* (1984) followed up patients atttending the infertility clinic to compare infertility in men with a history of undescended testes with the normal population.

All of these studies showed impaired fertility in such patients, should corrective surgery be unduly delayed. Early operation is therefore recommended, but the appropriate age for the procedure is still a matter for debate. This has gradually been reduced from pre-puberty to pre-school age over the last 2

Table 4 Age at First Paternity

	Below 19		*20–24*		*25–29*		*30–34*		*35–39*		*Above 40*		*Not known*	
Group	*Unil.*	*Bil*	*Unil*	*Bil*	*Unil*	*Bil*	*Unil*	*Bil*	*Unil*	*Bil.*	*Unil*	*Bil.*	*Unil*	*Bil*
A	—	—	—	—	—	—	1	—	—	—	—	—	—	—
B	—	—	9	2	9	4	3	—	—	—	—	—	—	—
C	2	—	6	1	6	1	1	1	—	—	—	—	—	—
D	—	—	3	—	2	—	1	—	1	—	2	—	1	—

decades and is now standard practice in most hospitals. In the early 1970s, electron microscopic evidence was presented to show degenerative changes which began as early as 2 years of age (Mengel *et al.*, 1974; Hadziselimovic *et al.*, 1975). Accordingly it was recommended that all patients be operated on before that age. Although some surgeons did perform orchidopexy on children below the age of 2 in the 1950s (Gross and Theodore, 1956), and many more adopted this approach after the electron microscopic evidence, most surgeons today are operating on these patients around pre-school age. The main reasons for this are:

1. The possibility of damaging the delicate vas and blood supply to the testis.
2. The carrying out of unnecessary operations on highly retractile testes, rather than cryptorchid testes, as reflected by the increasing numbers of such operations over recent years. In our hospital 271 orchiopexies were performed over a 10-year period after 1975, when we started operating on pre-school age children using the dartos pouch method, compared with only 192 operations between 1950 and 1975. Figures for the whole of Scotland show a similar increase (Campbell *et al.*, 1987).
3. Most surgeons remain unconvinced as to the correlation of electron microscopic findings with actual fertility, and whether the latter, which may already be satisfactory, will change at all by operating earlier.

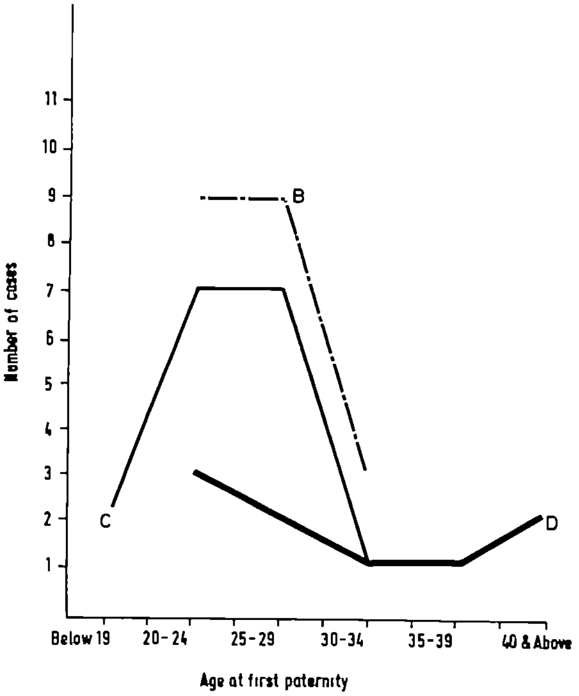

Fig. 3 Age at birth of first child in patients treated by unilateral orchiopexy.

Obviously the latter doubt has persisted because no statistics are available regarding normal values for male fertility. Atkinson *et al.* (1975) attempted to circumvent this problem by calculating percentage paternity, but were again confronted with the lack of normal figures for the male population. Therefore they compared their results with the available female statistics. We attempted to calculate percentage paternity along these lines—for unilateral cases in our study 83.9%, for bilateral cases 60% and for all cases 78.8%. These figures are appreciably higher than those reported by Atkinson *et al.* (1975) but, more importantly, are also higher than their standard normal of 74%, which they had derived from fertile marriages of women under the age of 45 years and married for at least 4 years in 1971. Our figures, like those of Atkinson *et al.* (1975), were calculated on the basis of any fertile marriage, and obviously would be even higher if only marriages over 4 years' duration were taken into consideration. We, therefore, did not find this approach very helpful.

Another drawback with previous studies is that none has studied fertility in relation to the age at operation. The average age of patients at the time of operation was used instead. In this study we have tried to focus on 2 aspects. First, that any such study must include various groups, according to age at operation. Second, age at the birth of the first child is probably a better index of fertility in men. If significantly different from that of the normal population, it could reflect a longer "trying" time (involuntary infertility) in such patients, who may not have abnormal semen analysis or testicular histology.

It must be admitted, however, that our atttempt to classify patients into 4 groups, according to age at operation, was only partially successful, because only 3 of 113 patients were operated on before the age of 6 years. Only 1 of these was married and had children.

The age of the father at the birth of his first child, however, seemed significant on finding that the percentage paternity was not very revealing. On plotting this, a curve similar to that in Figure 3 was produced. Female figures (General Register Office of Scotland, 1985) show that 75% have their first baby within the first 3 years of marriage and even younger in illegitimate cases. Considering that the pattern for males and females is the same in Figures 1 and 2, one would expect the same pattern in men with regard to first paternity. The average age at marriage in our cases was 25 years, so one would expect 75% to be fathers by 28 years of age.

The question of the optimal age for operation in patients with undescended testes will remain open to debate until a method is devised enabling the fertility of patients to be directly compared with that of the normal population. We have adopted a method which can be of value in this instance. It involves assessing the effect of operation on first paternity in the various groups to be compared and shows that only a very late operation, after 18 years of age, causes impaired fertility in unilateral cryptorchidism. Further studies are required to establish the reliability of this method, but it may prove helpful in the future, especially when the present under 2-year-olds achieve reproductive age and become available for comparison.

Acknowledgement

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Sperm Density Measurement: Should this be Abandoned?

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Summary—Sperm density measurement by means of the Makler chamber was performed on a single semen specimen from 2 groups: 104 proven fertile men and 53 infertile men; 11.5% of the fertile population had a sperm density <20 million/ml (median 84, mean 91.3, SD 60.5) and 33% of the infertile population had a sperm density >20 million/ml (median 10, mean 26.9, SD 34.8). There was a statistically significant difference in median between the 2 groups, but when a discriminant analysis was applied, sperm density could predict fertile status with only 68% accuracy at optimum cut-off. Sperm density is valueless in distinguishing fertile from infertile men and is neither useful in diagnosis nor in monitoring the progress of treatment for male infertility. It should be abandoned as a quotable measurement of male fertility.

Sperm density continues to be used routinely as a measure of semen quality and sperm function and changes in sperm density are still reported as if they were valid criteria of the fertile state. The term oligozoospermia is widely accepted to denote subfertility, taking sperm density of <20M/ml as its cut-off point.

The normal distribution of sperm density in proven fertile males has not been studied and the values usually quoted are based either on prevasectomy specimens often provided several years after supposedly fathering a child (Nelson and Bunge, 1974; David *et al.*, 1979) or on semen specimens produced while the partner was pregnant or had just given birth without any proof of paternity (Macleod and Gold, 1951; Macleod and Wang, 1979). Moreover, the measurement of sperm density may itself be inaccurate. There are considerable observer errors with the classical method of measurement by haemocytometer (Freund and Carol, 1964) and the rate of error is high within and between different observers examining the same specimen of semen (Jequier and Ukombe, 1983).

Previous studies comparing apparently fertile males with infertile males have usually included males from partnerships with a known female cause of infertility, which should have been excluded.

The true distribution of sperm density in a population of fertile men can only be determined if the method of measurement is known to be low in observer error and the paternity of the semen donor has been proven. In a previous study from this department the Makler chamber was found to have an acceptably low error when used by one experienced observer (Badenoch *et al.*, 1985). Establishing paternity is more difficult, but by using the known frequency distribution of HLA groups in the normal population it is possible to exclude a wrongly named father with >95.5% confidence (Terasaki, 1980).

Patients and Methods

Population 1

A total of 570 husbands of women in the maternity ward of the London Hospital were asked, after full explanation, to donate a specimen of semen and blood for this study; 113 men volunteered. All but 1 of these volunteers were successful in fathering a child within a period of 12 months of unprotected sexual intercourse. HLA-A, -B and -C antigens were determined from blood of the child's umbilical cord, the mother and the putative father. Using tables for the frequency distribution of these

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antigens in the population, it is possible to exclude paternity with >95./% confidence; 104 men fulfilled these criteria and were analysed. The semen was provided under standard conditions whilst the subject was physically well, after 3 days' sexual abstinence, by masturbation into a sterile plastic container, and examined within 4 h using the mean of 3 measurements made by a single observer with the Makler chamber.

Population 2

This group comprised 53 males with primary infertile marriages who had failed to conceive after 2 years or more of unprotected sexual intercourse. This excluded men with azoospermia and those whose female partners were shown to have a gynaecological cause of infertility. Semen was examined in the same way as in the first population.

Results

The age distribution of the 2 groups was comparable. The mean age for the fertile group was 29.2 years (SD 5.7) and for the infertile group 30.2 years (SD 4.6). The distribution of sperm density in the fertile population is shown in Figure 1; 11.5% of this population had a sperm density <20 M/ml. This compared with the infertile population, whose distribution is shown in Figure 2. Using a Mann-Whitney U test there was a significant difference between the 2 groups (P<0.001); there was also a significant difference in variability.

Using stepwise discriminant analysis (computer program BMD P7M) (Dixon *et al.*, 1981), sperm density results were analysed to determine how effectively sperm density distinguished the fertile group from the infertile and vice versa; 36% of the fertile group would be incorrectly classified as infertile and 25% would be incorrectly classified as fertile. Overall sperm density could discriminate with 68% accuracy at optimum cut-off of 35 M/ml. This is visually expressed in Figure 3, which shows the Receiver Operating Characteristic curve for the fertile population, plotting the true positive rate against the false positive rate. If a test is a good predictor of fertility the true positive/false positive ratio should approach unity. Clearly this is not the case, indicating that sperm density by Makler chamber is an insensitive diagnostic test. If a discriminant analysis of log sperm density with an optimum cut-off at 26.5 is applied, this improves the predictive value, so that 80% overall were correctly classified as fertile.

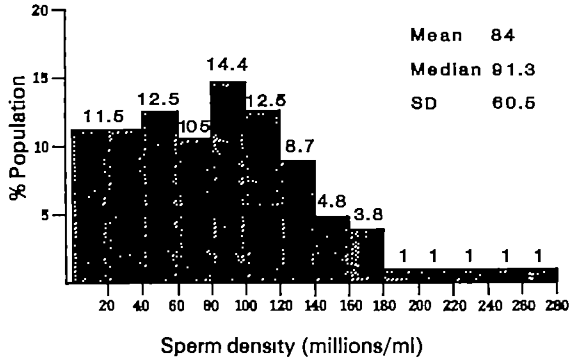

Fig. 1 Fertile males. Sperm density distribution.

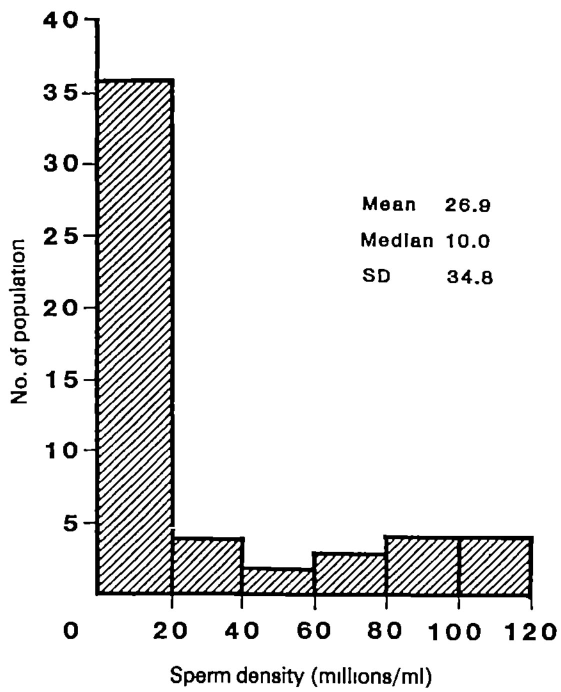

Fig. 2 Infertile males. Sperm density distribution.

Discussion

Macomber and Sanders (1929) suggested that there was a direct relation between sperm density and male fertility based on a study of 294 individuals; they also stated that with sperm density levels below 60 M/ml fertility was unlikely. Several studies have since looked at levels of sperm density in fertile and infertile populations. Perhaps the best known of these and most often quoted is that of MacLeod and Gold (1951), who studied 1000 men whose wives were pregnant at the time of semen analysis, although no proof of paternity was made. A parallel study of semen quality was made in 1000

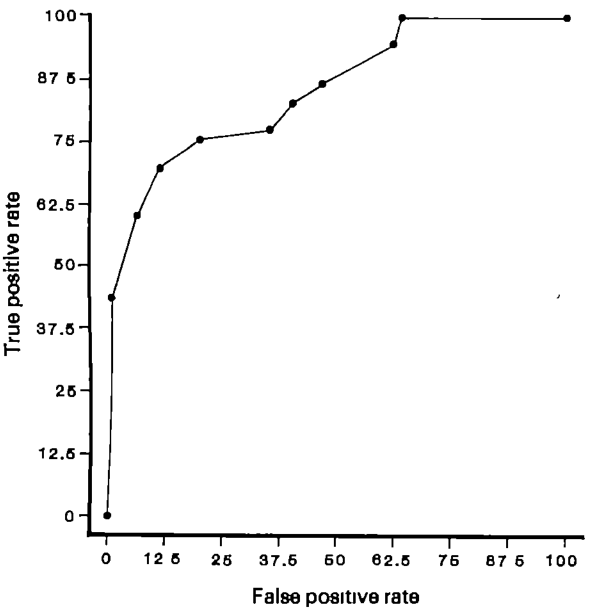

Fig. 3 Receiver operating characteristic (ROC) for sperm density.

cases of infertile marriages, couples whose period of infertility ranged from a few months to 15 years and included partnerships where a female cause for infertility had been shown and some with secondary infertility. The mean sperm density for the fertile group was 107 M/ml (SD 74) and for the infertile group 90 M/ml (SD 76). There was a significant difference between the 2 groups; only 5% of the fertile (compared with 16% of the infertile) males had a sperm density <20 million and it was suggested that this should be taken as a cut-off level below which either infertility or sub-fertility was indicated. Nelson and Bunge (1974) studied 386 men prior to undergoing vasectomy and found that 20% had a sperm density <20M/ml and only 7% had a sperm density >100 M/ml. This study was criticised by MacLeod and Wang (1979) because the semen was provided by men who may have fathered shildren several years before seeking vasectomy. Mortimer *et al.* (1983) showed that there may be considerable variations in levels of sperm density from one individual at different times.

Although the present study may be criticised because only one ejaculate per subject in either group was studied, and because the semen was provided 9 months after the time of conception, the real questions to be asked are whether sperm density offers a predictive guide to the quality of semen and thus the fertile state of the subject under study and whether there is any useful cut-off, whether it be 10, 20 or 30 million/ml.

This study shows sperm density to be extremely poor as a predictor of fertile state. Because of the large overlap in values between the 2 groups there can be no valid cut-off. Sperm density should no longer be used as a measure of semen quality and the misleading term oligozoospermia should be abolished.

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Is Routine Pre-treatment Cryopreservation of Semen Worthwhile in the Management of Patients with Testicular Cancer?

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Summary—Post-treatment fertility was evaluated in 147 patients with testicular cancer, All had pre-treatment sperm cell analysis following orchiectomy during the years 1979 to 1987. For only 17 patients was the question of future fertility of no importance. Pre-treatment semen cryopreservation was requested by 91 patients, but poor semen parameters made this procedure impossible in 38.

Of 99 evaluable patients, 44 had a post-treatment sperm count $\geq 10 \times 10^6$/ml and 22 of these fathered a child after treatment. Post-treatment fertility was observed to the same degree in patients who had pre-treatment semen cryopreservation as in those in whom this procedure could not be performed. Four of 53 patients used their deep-frozen semen but only 1 pregnancy resulted. The intensity of treatment, especially the extent of retroperitoneal surgery, had a significant effect on post-treatment fertility in the individual patient.

Pre-treatment cryopreservation of semen may be psychologically useful in patients with newly diagnosed testicular cancer, but its clinical significance is doubtful.

After the introduction of cisplatin-based chemotherapy, testicular cancer has become a curable malignancy (Fosså *et al.*, 1988). Treatment-related toxicity remains the price to be paid for a 90% cure rate. Most of the side effects are acute and reversible, but chronic toxicity has given rise to increasing concern. Gastrointestinal toxicity, neuropathy and infertility are the most significant long-term side effects.

Previous reports have dealt with the influence of different forms of treatment on fertility (Nijman *et al.*, 1982; Drasga *et al.*, 1983; Kreuser *et al.*, 1984; Fosså *et al.*, 1985a, b, 1986; Berthelsen, 1987; Lange *et al.*, 1987). Post-treatment fertility is affected by changes in sperm cell production (irradiation, cytostatics) and/or by disturbance of seminal fluid transport (retroperitoneal surgery). However, less is known of the frequency and the extent to which post-treatment fertility disturbances represent a clinical problem in patients cured of testicular cancer and to what degree pre-treatment semen cryopreservation reduces post-treatment fertility problems. These questions were therefore addressed in a series of 147 patients treated for testicular cancer.

Patients and Methods

During the years 1979 to 1987, 771 patients with newly diagnosed testicular cancer were referred to the Norwegian Radium Hospital: 172 underwent sperm cell analysis 3 to 60 days after orchiectomy and before further treatment. During the first 6 years sperm analysis was performed only rarely in patients without children, before diagnosis of their cancer. During the last 2 years all new patients were asked to undergo sperm analysis to evaluate the feasibility of sperm banking (70%) or for the purpose of clinical research (30%). All patients gave informed consent. This selection procedure has led to an over-representation of patients with non-seminoma in this series.

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Staging and treatment principles have been reported by Fosså *et al.* (1988). Briefly, patients with seminoma stage I or limited stage II received abdominal irradiation (36–40 Gy/3½–4 weeks). The median gonadol dose to the remaining testis was 50 cGy (range 21–140). Advanced metastatic seminoma was treated by cisplatin-based combination chemotherapy followed by radiotherapy or surgery. Non-seminoma patients underwent retroperitoneal surgery, which in the case of metastases was routinely combined with 3 to 4 cycles of cisplatin-based chemotherapy (median cisplatin dose 730 mg, range 200–1350). The criteria for retroperitoneal lymph node dissection (RLND) have been outlined previously (Fosså *et al.*, 1985a, b). RLND was performed unilaterally in patients with clinical stage I/IIa who per-operatively were found to be tumour-free. In all other patients with primary RLND, and in patients who had post-chemotherapy surgery, a bilateral operation was performed. Approximately 20% of the unilaterally treated patients, and virtually all patients after bilateral RLND, developed "dry ejaculation" post-operatively. Approximately one-third of such patients obtained antegrade ejaculation by the use of sympathicometics (Fosså *et al.*, 1985a).

By the end of 1987, 3 of the 172 patients had died. A questionnaire was sent to the surviving 169 patients containing 21 questions about pre- and post-treatment paternity and its associated psychological concerns; 161 disease-free patients completed the questionnaire by 31 December, 1987. Fourteen patients were subsequently excluded from the study because of "unconventional" treatment: they had received radiotherapy in addition to chemotherapy, and/or cytotoxic drugs other than cisplatin, vinblastine, bleomycin and/or VP16.

The remaining 147 patients were initially divided into the following groups (Table 1):

Group 1: Patients who at the start of treatment definitely wanted to father a child after treatment (n = 54).
Group 2: Patients who could not exclude future fatherhood (n = 76).
Group 3: Patients who at the start of treatment did not wish to become fathers at any time in the future (n = 17).

In 90 of these 147 patients 1 or several post-treatment sperm analyses were performed at least 12 months after treatment (median 14, range 12–63) either in the ejaculate or in the post-masturbation urine in case of "dry ejaculation".

The definition of pre-treatment normospermia was as follows: $\geq 20\times 10^6$/ml sperm cells, $\geq 40\%$ mobile sperm cells, mobility grade ≥ 2. The minimum criteria of sperm cell counts qualifying for semen cryopreservation were: $\geq 10\times 10^6$/ml sperm cell, $\geq 20\%$ mobile sperm cells, mobility grade ≥ 2.

Statistics

The statistical program package "Medlog" was used to calculate medians, means and ranges. Student's *t* test, the chi-square test and Wilcoxon

Table 1 Details of Patients and Clinical Parameters

	*Group 1**	*Group 2**	*Group 3**	*Total*
No. of patients	54	76	17	147
Median age (years)	26	26	44	27
Seminoma/non-seminoma	18/36	21/55	14/3	53/94
Stage 1	35	43	14	92
2	14	28	3	45
3	1	—	—	1
4	4	5	—	9
Treatment				
Surveillance	1	4	1	6
Irradiation only	18	20	13	51
Chemotherapy only	—	1	—	1
Unilat. RLND only	16	17	—	33
Unilat. RLND + chemotherapy	3	10	1	14
Bilat. RLND + chemotherapy	16	24	1	41
Thoracotomy + chemotherapy	—	—	1	1
Observation period (median)†	33	24	79	30

* Group 1: Positive wish for future paternity, Group 2: Future paternity could not be excluded; Group 3: Future paternity not planned † Months after cessation of treatment.

rank test were applied to assess differences. These were regarded as statistically significant if $P < 0.05$.

Results

Pre-treatment fertility status (Table 2)

Pre-treatment sperm cell analysis revealed no significant differences between the 3 groups. Cryopreservation of sperm cells was performed equally often in Groups 1 and 2. Significantly more patients in Groups 2 and 3 had had at least 1 child before the diagnosis of testicular cancer. Accordingly, pre-treatment infertility problems were observed more frequently in Group 1.

Table 2 Pre-treatment Fertility Status

Pre-treatment	*Group 1* (n=54)*	*Group 2* (n=76)*	*Group 3* (n=17)*	*Total (n=147)*
Paternity achieved	13	30	17	60
Paternity not achieved	11	8	—	19
Sperm analysis				
Normospermic	15	27	3	45
Hypospermic	29	37	10	76
Azoospermic	10	12	4	26
Semen cryopreservation				
Yes	23	30	—	53
No, poor semen parameters	19	19	—	38
No, not relevant	12	27	17	56

* See footnote, Table 1

Pre-treatment semen cryopreservation was requested by 91 men and this was performed in 53 (Group 4). In 38 patients pre-treatment sperm analysis showed poor semen parameters which did not allow cryopreservation (Group 5). For 56 patients the question of cryopreservation was irrelevant (little or no desire for future paternity or no fertility problems expected following radiotherapy only or surveillance) (Group 6).

Post-treatment fertility (Tables 3, 4, 5)

Thirty-seven patients attempted to father a child after treatment for testicular cancer, 28 of them in Group 1 (Table 3). Approximately half of the evaluated patients had post-treatment sperm counts $\geq 10 \times 10^6$/ml; 22 of 44 patients fulfilling this criterion fathered at least 1 child after treatment. Further analysis showed that patients with post-treatment sperm counts $< 10 \times 10^6$/ml had received significantly more chemotherapy (as assessed by the total dose of cisplatin) and frequently had "dry ejaculation" compared with patients with post-treatment sperm counts $\geq 10 \times 10^6$/ml (data not shown). The pre-treatment fertility status (number of children, normospermia) was similar for both types of patients.

Table 3 Post-treatment Fertility and Pre-treatment Desire for Future Paternity

Post-treatment	*Group 1* (n=54)*	*Group 2* (n=76)*	*Group 3* (n=17)*	*Total (n=147)*
Paternity attempted	28	9	0	37
Sperm count $\geq 10 \times 10^6$/ml	20/35†	20/45	4/10	44/90
Paternity among patients with post-treatment sperm counts $\geq 10 \times 10^6$/ml	14	6	2	22

* See footnote, Table 1.
† No of patients with $\geq 10 \times 10^6$ per ml/no. of evaluated patients.

Table 4 Post-treatment Fertility and Semen Cryopreservation in Patients with Testicular Cancer

Post-treatment	*Group 4* (n=53)*	*Group 5† (n=38)*	*Group 6‡ (n=56)*	*Total (n=147)*
Paternity attempted	16	12	9	37
Sperm count§ $\geq 10 \times 10^6$/ml	16/37	13/27	15/26	44/90
Paternity among patients with post-treatment sperm counts $\geq 10 \times 10^6$/ml	7	5	4	16
Deep frozen semen used	4			4

* Pre-treatment cryopreservation performed.
† No cryopreservation due to poor pre-treatment semen quality/quantity. ‡ Cryopreservation not relevant § No of patients with $\geq 10 \times 10^6$/ml/no of evaluated patients.

The percentages of patients who achieved post-treatment paternity or sperm counts $\geq 10 \times 10^6$/ml were 43% for patients in whom pre-treatment semen cryopreservation had been performed (Group 4), 48% for patients with poor pre-treatment semen parameters (Group 5), and 58% for patients in whom the question of semen cryopreservation had been irrelevant (Group 6) (Table 4).

Four of 53 men tried to become fathers by using their own cryopreserved sperm cells. This resulted in 1 pregnancy (Table 5). "Dry ejaculation" represented the main problem in the remaining 3 patients and this was reversed by the use of sympathicomimetics in 2 (after the unsuccesful use of deep-frozen semen). Both patients achieved paternity when taking sympathicomimetics. "Dry

Table 5 Outcome of Artificial Insemination with Cryopreserved Semen

			Pre-treatment			
Patient no.	*Age (years)*	*Histology*	*Sperm count**	*No of trials*	*Pregnancy*	*Fertility problems*
1	38	Seminoma	60	2	Yes	Paternity wanted < 1 year after radiotherapy
2†	27	Non-seminoma	87	4	No	"Dry ejaculation"
3†	28	Non-seminoma	25	6	No	"Dry ejaculation"
4	21	Non-seminoma	17	3	No	"Dry ejaculation"

* $\times 10^{6}$/ml

† Antegrade ejaculation by sympathicomimetics resulting in sperm cell count $> 10 \times 10^{6}$/ml or achievement of 2 pregnancies (Patient no. 3).

ejaculation" also represented the main problem in 9 of 13 patients who, after treatment, failed to become fathers (Table 6).

Discussion

In the present study, 37% of patients expressed a desire for future fatherhood at the time of diagnosis. This figure confirms the results from a prospective series from the Norwegian Radium Hospital (Nina Aass, unpublished results): 27 of 79 men (34%) stated definitely at the time of diagnosis of testicular cancer that they wanted to father a child in the future, and 37 of the 82 patients admitted that they were afraid of becoming infertile after treatment. As in the present study, both groups contained men in their fourth decade. A changing social structure, which involves many men either marrying for the first time in their forties, or re-marrying, makes the question of post-treatment fertility important for testicular cancer patients in this age group.

In the present series, 13% of patients with newly diagnosed testicular cancer had been unsuccessful in their attempts to father a child before diagnosis of their malignancy. This underlines the hypothesis that infertility may be related to the aetiology of testicular cancer (Skakkebæk, 1978). It is interesting that 5 of 9 men with pre-treatment fertility problems succeeded in becoming fathers after treatment.

Table 6 Patients who Failed to Achieve Fatherhood after Treatment (to Dec. 1987)

Pre-treatment			*Post-treatment*			
Patient no	*Infertility*	*Sperm cell count**	*Gy*	*Cisplatin (mg)*	*"Dry ejaculate"*	*Sperm cell count**
1	?	50	—	760	Yes	—
2	Yes	87	—	—	(Yes)†	222‡
3	Yes	0	—	400	(Yes)	17
4	?	13	—	—	Yes	—
5	?	6	—	720	Yes	Urine + §
6	No	49	—	510	Yes	Urine +
7	?	17	—	600	Yes	—
8	?	0	—	600	Yes	—
9	No	6	—	800	Yes	—
10	No	108	—	800	Yes	Urine +
11	Yes	4	36	—	No	36
12	Yes	6	36	—	No	67‡
13	?	1	40	—	No	2
14	?	24	40	—	No	2
15	?	1	—	—	No	1

* $\times 10^{6}$/ml. † ( ) Reversed by sympathicomimetic drugs ‡ Pregnancy achieved in 1988 § Sperm cells in post-masturbation urine.

Within the observation period, approximately half of the patients who wished to become fathers after treatment have either succeeded or have had a sperm cell count ($\geq 10 \times 10^6$/ml) which is associated with a resonable probability of pregnancy (Stanwell-Smith and Hendry, 1984; Hargreave and Elton, 1986). The incidence of eventual pregnancies seems acceptably high: 22 of 37 men became fathers. For some of the patients in the present series the observation period is short and the pregnancy rate may increase with the passage of time.

The present results indicate that it is primarily the treatment which determines post-treatment fertility. The results of pre-treatment sperm cell analyses, the suitability of the patient for semen cryopreservation and even the incidence of pre-treatment infertility problems correlated to a much lesser degree with the incidence of post-treatment paternity. These results are consistent with recently published observations in patients with Hodgkin's disease (Redman *et al.*, 1988). In the modern treatment of testicular cancer, the extent of RLND seems to have a significant effect on post-treatment fertility.

It has been shown that both radiotherapy and chemotherapy permit recovery of spermatogenesis within 3 years of discontinuing treatment in the majority of patients (Nijman *et al.*, 1982; Drasga *et al.*, 1983; Kreuser *et al.*, 1984; Fosså *et al.*, 1985a, b, 1986; Berthelsen, 1987; Lange *et al.*, 1987). This is confirmed in the present study. The main problem in patients with post-treatment fertility problems seems to be "dry ejaculation" resulting from retroperitoneal surgery (Whitmore, 1982). Every attempt should therefore be made to restrict such surgery to the less extensive and ejaculation-preserving procedures, or to omit diagnostic RLND whenever possible (Fosså *et al.*, 1985a, b; Pizzacaro *et al.*, 1985; Lange *et al.*, 1987; Donohue *et al.*, 1988; Jewett *et al.*, 1988).

A trial with sympathicomimetics should be offered to all patients with "dry ejaculation". Our success rate with such treatment is higher than some published results (Nijman *et al.*, 1982) and may be related to our attempt to limit the extent of RLND as much as possible. Other means of overcoming problems with seminal fluid transport may be electrostimulation (Bennett *et al.*, 1987), corrective plastic surgery (Middleton and Urry, 1986) or the formation of an artificial spermatocele (Brindley *et al.*, 1986) in order to obtain vital sperm cells. Though such sperm cells are often less mobile and viable, especially if chemotherapy and/or radiotherapy has been used in addition to surgery, they can be used for artificial *in vivo* or *in vitro* insemination (Cohen *et al.*, 1985).

Should cryopreservation be offered routinely to patients with testicular cancer? The present results indicate that its benefits are limited. Post-treatment sperm counts $\geq 10 \times 10^6$/ml were observed to the same extent in patients whose pre-treatment sperm cell counts allowed cryopreservation as in those who could not be offered sperm banking due to poor pre-treatment sperm counts. Semen cryopreservation thus seems to be unnecessary for the majority of testicular cancer patients who hope to achieve fatherhood after treatment, especially since modern treatment regimens are considerably less toxic than they used to be. In addition, as shown by Reed *et al.* (1986), the success rate in obtaining pregnancies using deep-frozen semen seems to be low, even if the criteria for cryopreservation are more rigorous than in the present study (for example, requiring a sperm cell density of at least 20×10^6/ml). It is therefore doubtful whether a cost–benefit analysis would justify the routine use of pre-treatment semen cryopreservation for all testicular cancer patients, especially if the patients has to travel 1000 km for sperm banking, as is the case in Norway at present. As shown in previous reports and confirmed in the present study, only 50 to 60% of patients with newly diagnosed testicular cancer present with sperm counts allowing semen cryopreservation (Bracken and Smith, 1980; Fosså *et al.*, 1984). On the other hand, for individual patients requiring very intensive treatment, deep-frozen semen may represent the only chance of fathering a child. Furthermore, the psychological importance of pre-treatment semen cryopreservation should not be overlooked.

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Chemotherapy of Advanced Seminoma: Clinical Significance of Radiological Findings before and after Treatment

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Summary—The predictive significance of the mass detected following chemotherapy was assessed in 46 patients with advanced seminoma. Patients with residual viable seminoma in the post-chemotherapy operation specimen or who developed recurrent disease were regarded as chemotherapy failures. This group included 1 of 20 patients in whom the retroperitoneal masses were ≤ 10 cm^2 3 to 4 weeks after chemotherapy and 4 of 15 patients whose residual masses were > 10 cm^2.

Four of 11 patients with mediastinal tumours achieved a complete remission (mediastinal masses ≤ 1 cm^2). However, 2 of these 4 patients relapsed, as did 2 of the 4 who achieved a partial remission. In no case was the original size of the tumour significantly related to treatment failure. Three patients had residual lung masses; 1 of these contained histological evidence of viable tumour.

In one-third of the irradiated relapse-free patients, slightly enlarged masses were visible on follow-up computed tomography scans taken several years after treatment, even in patients without tumour activity.

There is a 25% risk of relapse in patients with advanced seminoma who have retroperitoneal masses > 10 cm^2 following cisplatin-based chemotherapy. They should be followed up regularly for many years.

Recent reports have demonstrated that patients with advanced metastatic seminoma should be treated with cisplatin-based induction chemotherapy as their initial treatment (Wajsman *et al.*, 1983; van Oosterom *et al.*, 1984; Friedman *et al.*, 1985; Peckham *et al.*, 1985; Fosså *et al.*, 1987; Loehrer *et al.*, 1987). It is still debatable whether consolidation treatment—surgery or radiotherapy—should be given and when (Fosså *et al.*, 1987; Motzer *et al.*, 1987; Schultz *et al.*, 1988). Several authors have reported residual masses for long periods after chemotherapy (Friedman *et al.*, 1985; Peckham *et al.*, 1985; Fosså *et al.*, 1987) and it is claimed that such masses shrink very slowly. Histologically, most of these masses contain fibrosis or necrosis. Only occasionally is viable malignant tumour tissue found.

The present retrospective study deals with the clinical significance of radiological findings in patients with advanced seminoma before and after chemotherapy and after consolidation treatment. The main question was whether, and to what extent, the radiological findings before and after treatment could predict the response to chemotherapy.

Patients and Methods

Patients were eligible for inclusion in the study if they fulfilled the following criteria. (1) They had advanced metastatic pure seminoma. (2) They were treated with at least 3 cycles of cisplatin-based induction chemotherapy as previously described

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(Fosså *et al.*, 1987). (3) They had a CT scan before and after treatment, thus permitting measurement of the metastatic lesion. (4) In patients with previous radiotherapy, only non-irradiated lesions were considered. Table 1 gives details of the 46 eligible patients treated between 1979 and 1986. Clinical staging was carried out according to the Royal Marsden classification system (Peckham *et al.*, 1979).

In general, the CT scan was performed immediately before starting chemotherapy, 3 to 4 weeks after the last cycle, 8 to 12 weeks after consolidation treatment and—in the case of residual masses—at yearly intervals.

Computed tomography was performed on a GE CT T 8800 scan unit. Scan thickness was 10 mm. Contiguous slices were used in the chest and 10 mm unscanned intervals were used in the abdomen (Lien *et al.*, 1987).

In the first investigation (before starting chemotherapy) the largest tumour was identified. Maximum diameters at a 90° angle were recorded (cm) and the product of these (cm^2) gave the size of the tumour. Tumours were located in the retrocrural space, the upper lumbar region (above the left renal vein), the lower lumbar region and the iliac region (below the aortic bifurcation) as well as in the mediastinum and lungs. The same tumours were measured in the follow-up examinations.

The main consolidation treatment after chemotherapy was radiotherapy to the initial tumour-bearing area: 36 to 40 Gy were given to opposing abdominal and/or mediastinal fields. However, in 1980 and 1981 there was a period during which it was of interest to obtain post-chemotherapy histology. A few additional patients received post-chemotherapy surgery during the latter part of the trial. A total of 11 patients had retroperitoneal surgery after induction chemotherapy. In 2 patients thoracotomy was performed after chemotherapy with resection of residual lung masses.

Table 1 Details of Patients and Treatment

Median age (years)	37
Previous radiotherapy	8
Lesions	
Retroperitoneal tumour	35
Mediastinal tumour	11
Lung metastases	3
No of cycles: 3	5
4	38
5	3
Medial observation time (months)	37
Median interval (weeks) between:	
(1) Pre-chemotherapy and first post-chemotherapy CT scan	15
(2) First post-chemotherapy and first post-consolidation CT scan	16

After radiotherapy or surgery no further treatment was given to patients with no evidence of recurrent disease except for 1 patient with a histologically confirmed seminoma who received post-operative abdominal radiotherapy.

Follow-up examinations were performed at 2–6-monthly intervals for 5 years and included clinical examination, chest X-ray, serum tumour marker determination and CT scan.

The principal end point of the analysis was failure of induction chemotherapy to render a patient tumour-free, as evidenced by residual seminoma in the operation specimen or by recurrent disease.

Results

Before treatment the retroperitoneal tumour measured between 6 and 400 cm^2 (Table 2, Fig. 1). Induction chemotherapy led to a significant reduction in all tumour masses, although residual tumours (>1 cm^2) were found in 26 of 35 patients (10 of 11 in the surgery group and 16 of 24 in the radiotherapy group). In 20 patients the residual mass after chemotherapy was ≤ 10 cm$_2$ and in 15 patients it was >10 cm^2. Surgery led to normal CT findings (defined as area ≤ 1 cm^2) in all patients, whereas the residual masses at the first CT scan following radiotherapy were >1 cm^2 in 11 of 24 patients. In addition, 9 of 24 patients had enlarged retroperitoneal lymph nodes at the last follow-up CT examination.

Table 2 Size of Retroperitoneal Tumour and Clinical Outcome

	Median tumour size (cm^2)		
Time of CT	*Surgery (11)*	*Radiotherapy (24)*	*Total (35)*
Before chemotherapy	76	40	47
After chemotherapy	10	4	6
After consolidation treatment	0	4	0
Chemotherapy failure*	2	3	5
Dead of seminoma	1	2	3

*Viable seminoma in post-chemotherapy operation specimen or subsequent relapse.

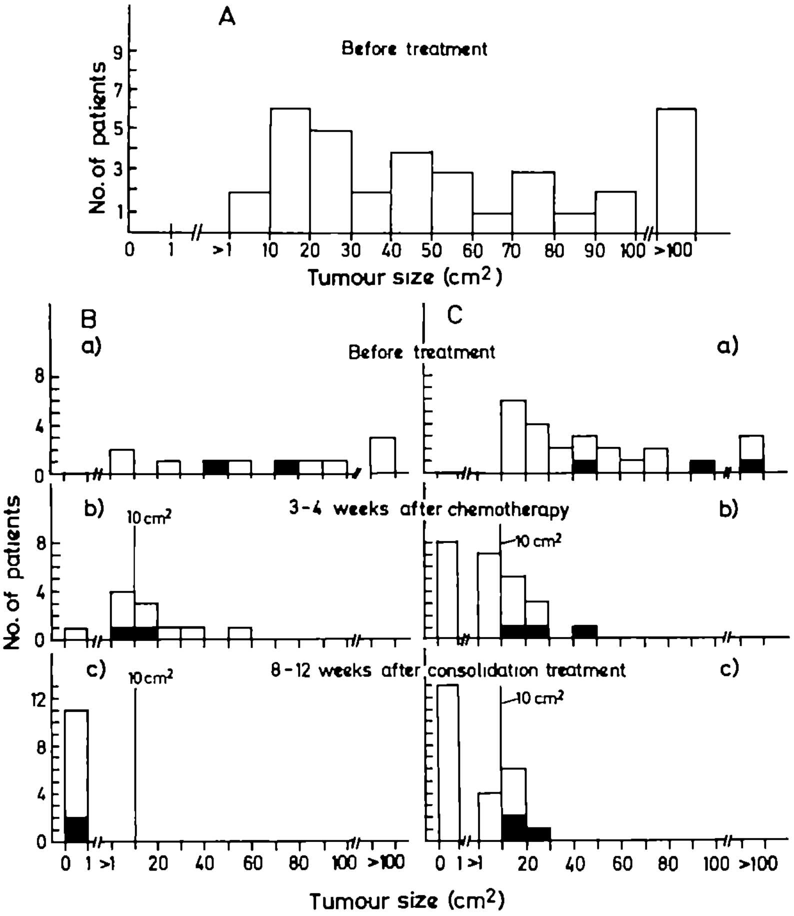

Fig. 1 Size of retroperitoneal tumour and results of treatment in advanced metastatic seminoma. (A) All retroperitoneal tumours (n = 35) (B) Retroperitoneal tumours with post-chemotherapy surgery (n = 11) (C) Retroperitoneal tumours with post-chemotherapy radiotherapy (n = 24) ■ patients who failed to respond to chemotherapy.

Two patients in the surgery group had viable seminoma in the post-chemotherapy operation specimen. After radiotherapy 3 patients relapsed; in all cases the tumours were outside the radiation field. Four of these 5 patients had a reduction of at least 50% in their retroperitoneal tumour during chemotherapy (Table 3). In the fifth patient the reduction was 49%. When compared with patients who responded to chemotherapy, the initial size of the tumour and its reduction following chemotherapy were not related to the outcome of cytostatic treatment. However, the residual retroperitoneal mass after chemotherapy was >10 cm^3 in 4 of the 5 patients with chemotherapy failure.

In 7 of the 11 patients with mediastinal tumours, residual masses larger than 1 cm^2 were present after chemotherapy (Table 4, Fig. 2). At the last CT scan, 4 of the 11 patients still had tumour masses >1 cm^2 and 4 patients relapsed. All had received mediastinal irradiation following chemotherapy. The site of the first relapse was outside the radiation field in all 4 patients. Of the 4 relapsing patients, 2 had enlarged mediastinal lymph nodes (>1 cm^2) after their primary treatment.

Only 3 patients with residual lung masses were investigated. It was not possible to relate the response to chemotherapy to the initial size of lung metastases or the degree of tumour reduction. All remaining lung masses were <1 cm^2. In 1 patient the residual lesion contained viable malignant tumour tissue. In the second surgically treated patient the metastasis was completely necrotic. The lesion in the third patient (who did not undergo surgery) has remained stable for 3 years.

Table 3 Size of Tumour Initially and Following Chemotherapy in Patients with Retroperitoneal Tumours

Patient no.	*Initial size (cm²)*	*Reduction %*	*Consolidation*
Treatment failure*			
1	76	91	Surgery
2	49	49	Surgery
3	47	76	Radiotherapy
4	162	83	Radiotherapy
5	97	58	Radiotherapy
No chemotherapy failure			
Median	91	83	
Range	(6–400)	(69–94)	Surgery (9 patients)
Median	31	90	
Range	(11–180)	(59–100)	Radiotherapy (21 patients)

*Viable seminoma in the post-chemotherapy operation specimen or recurrence.

Table 4 Size of Mediastinal Tumour and Results of Treatment in 11 Patients

Time of CT	*Tumour size (cm²)*
Before chemotherapy	23 (6–130)
After chemotherapy	3 (0–24)
After consolidation treatment	2 (0–28)
Chemotherapy failure	4
Dead of seminoma	4

Discussion

Eight of the 46 patients with advanced seminoma were not cured by the initial treatment, an incidence similar to that reported by other workers (Wajsman *et al.*, 1983; van Oosterom *et al.*, 1984; Friedman *et al.*, 1985; Peckham *et al.*, 1985; Loehrer *et al.*, 1987).

Several authors have tried to define radiological parameters which before treatment or at an early stage of therapy are predictive of the final response to chemotherapy (Loehrer *et al.*, 1987; Motzer *et al.*, 1987; Schultz *et al.*, 1988). The pre-treatment extent of disease may be one predictive factor (Loehrer *et al.*, 1987). Motzer *et al.*, (1987) found that post-chemotherapy masses with a diameter >3 cm had a significantly increased probability of containing malignant seminoma. Schultz *et al.* (1988) were unable to confirm these findings in patients treated with cisplatin-based chemotherapy or carboplatin. In our series of 11 patients with

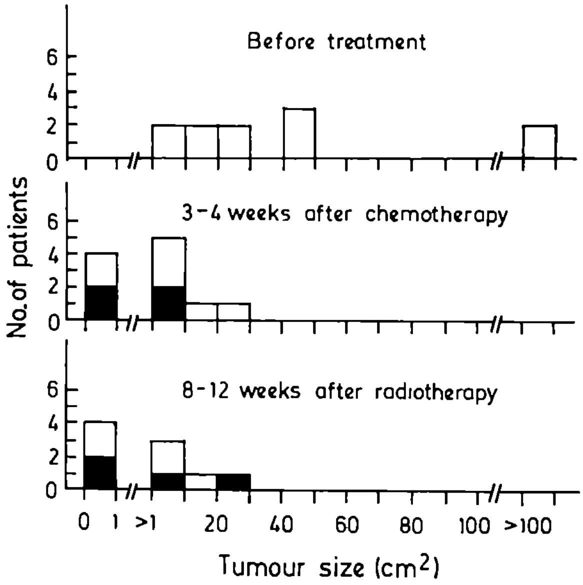

Fig. 2 Size of mediastinal tumour and results of treatment in advanced metastatic seminoma. ■ patients who failed to respond to chemotherapy.

retroperitoneal tumours treated surgically, 1 chemotherapy failure was found in 5 patients who after chemotherapy had residual masses >10 cm² and 1 among 6 patients with residual masses ≤ 10 cm². In the radiotherapy group, 15 patients had residual masses ≤ 10 cm² after chemotherapy. None of these 15 patients has relapsed. On the other hand, 3 of 9 patients with residual lesions >10 cm² developed a recurrence beyond the retroperitoneal space after chemotherapy failure. Combining the results of post-chemotherapy CT from both groups suggests that residual lesions measuring more than 10 cm² after chemotherapy (4/15 patients) represent a higher risk of failure than retroperitoneal masses $\leqslant 10$ cm² (1/20 patients) (P: 0.1, chi-square test.) These results confirm the observations of Motzer *et al.* (1987). The initial size of the retroperitoneal tumour *per se* and the degree of reduction after chemotherapy, however, do not appear to be factors which can predict the final outcome.

The situation is more complicated regarding mediastinal masses or lung metastases. A normal mediastinal CT scan (tumour area ≤ 1 cm²) after chemotherapy or post-chemotherapy lung masses <1 cm² do not exclude residual tumour or subsequent relapse.

The role of local consolidation treatment after cisplatin-based chemotherapy has been discussed previously (Wettlaufer, 1984; Friedman *et al.*, 1985; Fosså *et al.*, 1987; Motzer *et al.*, 1987; Schultz *et al.*, 1988). Retroperitoneal surgery is often technically difficult after chemotherapy and should be avoided. Radiotherapy is the alternative treatment. Most clinicians feel, however, that consolidation treatment—either radiotherapy or surgery—may be omitted if the patient can be controlled regularly after induction chemotherapy. On the other hand, our findings indicate that radiotherapy produces an additional local anti-neoplastic effect. Two of 11 post-chemotherapy specimens contained viable seminoma, whereas no local relapse was observed in 34 irradiated lesions (abdominal or mediastinal), although 5 of the irradiated patients developed recurrent disease elsewhere.

After radiotherapy only moderate additional shrinkage of the tumour can be expected. It is important to recognise that 9 of 28 irradiated tumours were >1 cm^2 at the last CT scan (retroperitoneal 7 of 21; mediastinal 2 of 7). These 9 patients have remained free of recurrence following primary treatment.

Failure of chemotherapy is to be expected in about 25% of patients who, after cisplatin-based induction chemotherapy, have residual retroperitoneal masses >10 cm^2. The size of mediastinal lymph nodes of long metastases following chemotherapy cannot be used as a predictor of chemotherapy failure. Radiotherapy to residual masses seems to decrease the risk of local tumour regrowth but does not prevent relapses outside the radiation field.

Radiotherapy leads only to moderate additional tumour shrinkage after chemotherapy. In one-third of irradiated, apparently tumour-free patients, residual masses will remain over long periods of time. If no surgery is performed, such patients should have follow-up CT scans at least once a year for several years in order to diagnose tumour regrowth at an early stage.

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Deep Dorsal Vein Arterialisation in Vascular Impotence

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Summary—A series of 12 patients with vasculogenic impotence (4 arterial lesions; 8 arterial and venous lesions) underwent deep dorsal vein arterialisation after pre-operative assessment by a multidisciplinary approach. Cumulative graft patency was 58% (7 of 12 patients) up to 21 months but only 4 patients developed almost normal erections.

Digital angiography, with and without the intracavernous injection of papaverine, was performed during follow-up to determine the vascular physiological status. At flaccidity, the corpora cavernosa were never opacified in the absence of a venocorporeal shunt. The penile glans was always visualised. Opacification of the deep dorsal vein and the circumflex system decreased with penile rigidity, resulting from their compression between Buck's fascia and the tunica albuginea. Intracavernous pressure recorded before and after the surgical procedure showed a marked increase when a caverno-venous shunt was performed. Hypervascularisation of the glans occurred in 2 cases. The relevance of this new surgical technique and its functional mechanism are discussed.

Several surgical techniques are applicable in the treatment of arterial impotence due to distal occlusive disease. These include penile protheses and revascularisation. Although penile implants give satisfactory results, the procedure is not physiological despite the development of inflatable devices that restore a more natural penile aspect. Several techniques using revascularisation of the penis have been described (Shaw and Zorgniotti, 1984). Direct methods provide arterial inflow directly into the corpora cavernosa, whereas indirect techniques use arterial shunting to the penile arteries. In bypassing the physiological arterial system, direct corporeal revascularisation procedures do not give encouraging long-term success rates. The high post-operative intracavernous pressure leads to microfibrosis of the erectile tissue and rapid thrombosis of the anastomosis. Post-operative priapism often occurs with this method. Indirect revascularisation of the penis offers several advantages: the new arterial blood flow into the corporeal bodies remains under vasomotor control of the penile vessels and the systemic systolic blood is not directed in a sustained fashion into the sinusoid spaces. However, the development of distal arterial disease is not prevented, which means that the best results are obtained following traumatic lesions (L'Hermitte *et al.*, 1983). In addition, these techniques do not take into account the role of the venous system and its possible disturbance. Caverno-venous leakage often occurs in association with arterial pathology in vascular impotence (Wespes and Schulman, 1987).

Deep dorsal vein (DDV) arterialisation, first described for patients with a venous leak (Virag, 1981), has been applied to both arterial and venous impotence (Balko *et al.*, 1986; Bennet *et al.*, 1986; Austoni *et al.*, 1987). Modifications of the initial technique have been introduced by creating a venous-corpora shunt (circumflex vein anastomosed to the neighbouring corpus cavernosum) or by ligating the DDV proximally.

We report our experience of DDV arterialisation in patients with arterial or mixed (venous and arterial) disease and present objective data to explain its functional mechanism.

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Patients and Methods

Selection of patients

The series comprised 12 patients aged between 37 and 58 years (mean 49) with erectile dysfunction secondary to arterial insufficiency or a combination of venous and arterial disease. Dynamic cavernography demonstrated cavernous-venous leakage in 8 patients because the flow necessary to create and to maintain an erection was higher than 120 and 40 ml/min respectively (Table) (Wespes *et al.*, 1984). The penile arteries were first studied by Doppler examination and the penile brachial systolic index was abnormal in every case (PBI <0.75). Because this study was performed on the flaccid penis, it was difficult to predict the functional ability of the penile arteries during erection. Selective pudendal arteriography was therefore performed after the intracavernous injection of 60 mg papaverine in patients who were candidates for penile reconstructive surgery (Table) (Delcour *et al.*, 1988). Papaverine induced the vasodilatation necessary to opacify arteries of small calibre and stretch penile arteries that were tortuous in the flaccid state, thereby allowing a good morphological study to be performed. All patients had severe bilateral stenosis of the penile arteries and 2 had complete thrombosis of a cavernous artery.

Neurological examination was carried out to exclude underlying disease. Testosterone levels were normal.

Technique

An incision was made along the lateral border of the right rectus muscle from just below the umbilicus to the base of the penis. The lateral border of the rectus muscle was mobilised. The epigastric pedicle was carefully dissected and the collaterals ligated with 4/0 silk.

When a sufficient length of inferior epigastric artery had been dissected, the pedicle was cut and ligated distally with 2/0 silk. A vascular clamp was placed on the free end of the pedicle but the veins running along the artery were ligated. A suprapubic incision was made at the base of the penis. The small dorsal superficial penile veins were not always ligated. Buck's fascia was incised longitudinally on the deep dorsal vein. Care was taken to preserve dorsal arteries and nerves. The DDV vein was dissected along a 3 cm length and the perforating veins tied with 4/0 silk sutures.

An oval piece of wall in the DDV was resected and the valves in the DDV were destroyed. A vascular clamp was placed at each end of this incision.

A termino-lateral anastomosis with the epigastric artery spatulated and the DDV was made in 10 patients with 8/0 nylon sutures using microscopic magnification. In 6 patients the deep penile vein was also ligated proximally; in 2 of these patients with severe arterial lesions (stenosis of one cavernous artery and occlusion of the other), an opening was made between the distal end of the arterialised DDV and the corpora cavernosa.

In 2 patients a termino-terminal anastomosis was made after transection of the DDV.

A heparin solution was used during the surgical procedure but the patient was not heparinised. Papaverine was also used to relax the arterial smooth musculature of the vessels, thus facilitating the anastomosis.

Graft patency was established immediately in the operating theatre by DDV palpation or with the Doppler stethoscope. The intracavernous pressure was measured before and after the surgical procedure. Digital angiography through a femoral artery approach was performed between the fifth and tenth post-operative days to assess the new penile vascularisation. In 1 patient, control angiography was performed 1 month later, before and after the intracavernous injection of 60 mg papaverine. During follow-up, patency was evaluated by Doppler examination at regular intervals. Clinical results were evaluated by assessing the patient's sexual life. Patients complaining of persistent erectile failure with a patent anastomosis underwent nocturnal penile plethysmography to exclude psychological problems.

Results

All anastomoses were patent at the end of the surgical procedure. The basal intracavernous pressure (7 mmHg; 4–9) was not modified when the anastomosis was termino-lateral (8 mmHg; 5–9) (Fig. 1) but increased slightly when the anastomosis was termino-terminal or when the DDV was ligated proximally (14 mmHg; 12–16) (Fig. 2). It increased significantly when a caverno-venous fistula was performed (25 and 30 mmHg) (Fig. 3). Mild penile oedema was observed in 2 patients but this resolved spontaneously within 15 days. Penile enlargement occurred in 1 patient with a caverno-venous fistula but there was no priapism. Cumulative graft patency was 58% (7 of 12 patients) at 21 months (range 6–21; mean 14).

Thrombosis of the anastomosis was observed in

Table Vascular Assessment, Surgical Procedure and Results

Patient no.	*Age (years)*	*Cavernometry: flows to create and maintain erection (ml/min)*		*Type of anastomosis*	*Follow-up (months)*	*Graft patency*	*Functional result*
1	37	180	90	T-L	21	+	+
2	55	140	80	T-L	6	+	+
3	39	120	50	T-L	15	–	–
4	52	180	60	T-L	14	+	–
5	42	180	80	T-T	19	+	+
6	58	120	40	T-T	15	–	–
7	52	180	70	T-L with lig.	12	–	–
8	53	200	100	T-L with lig.	13	–	–
9	48	200	120	T-L with lig.	12	+	+
10	54	180	60	T-L with lig.	10	+	–
11	38	180	90	T-L with lig. +C.V.	14	+	–
12	57	120	40	T-L with lig. +C.V.	6	–	–

T-L: termino-lateral anastomosis.
T-T: termino-terminal anastomosis
With lig: proximal ligature of DDV.
CV: caverno-venous fistula.

5 cases; in the immediate post-operative period in 2 patients, after 1 month in 1 and after 3 and 6 months in 2 patients.

Digital angiography revealed opacification of the DDV and the circumflex system but in no case were the corpora cavernosa opacified in the absence of a caverno-venous fistula (Figs 1, 2 and 3). Even when papaverine was injected intracavernously there was no opacification of the corpora cavernosa. Moreover, DVV opacification diminished with the development of penile rigidity induced by papaverine (Fig. 4). Four patients developed almost normal erections, 2 improved slightly and a poor result was observed in the remaining 6. Among

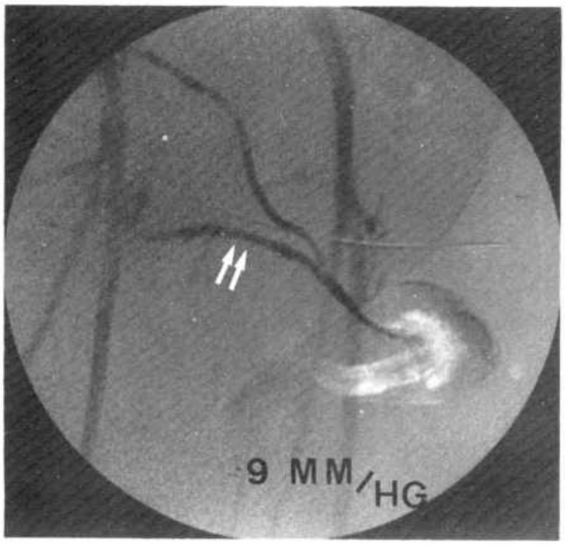

Fig. 1 Termino-lateral anastomosis of epigastric artery into deep dorsal vein (DDV) (↗↗). Corpora cavernosa are not opacified while glans and corpus spongiosium are visualised. Intracavernous pressure 9 mmHg.

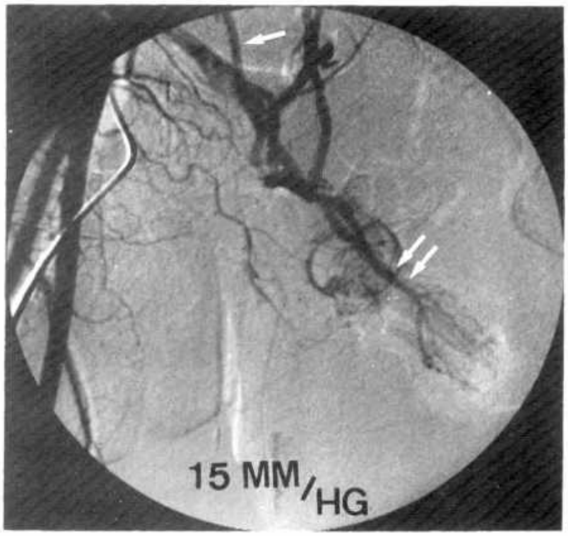

Fig. 2 Termino-terminal anastomosis of epigastric artery (↗) into DDV (↗↗). Good visualisation of circumflex system and glans but corpora cavernosa are not opacified. Intracavernous pressure 15 mmHg.

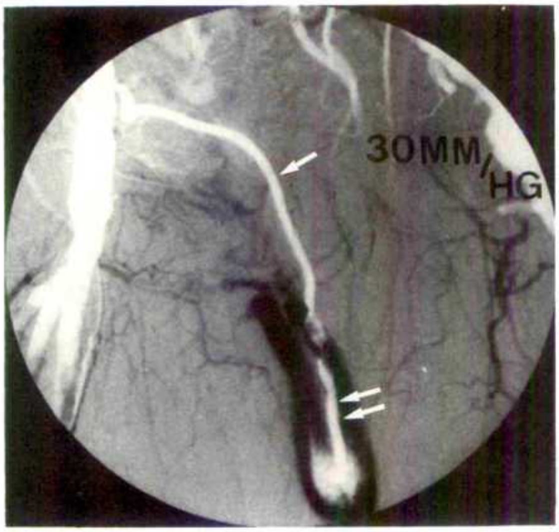

Fig. 3 Termino-lateral anastomosis of epigastric artery (↗) into DDV (⇗) with proximal ligation of vein and distal caverno-venous fistula. Corpora cavernosa are well opacified. Intracavernous pressure 30 mmHg.

these 6 patients, 3 had patent anastomoses but had no normal nocturnal erections during penile plethysmography.

Glans hypervascularisation was present in 2 patients in the immediate follow-up period.

Discussion

Although the present series was small, several conclusions can be drawn.

Although patency was achieved in 58%, only 4 patients (33%) developed almost normal erections for satisfactory intercourse. Thrombosis of the anastomosis did not seem to correlate with the degree of vascular abnormality or with the type of microscopic surgery (Table). Psychogenic factors accompanying the organic vascular cause could explain this discrepancy. However, these impotent patients with patent anastomoses had no nocturnal erections during penile plethysmography. The psychological factor could not therefore be responsible for these failures.

Deep penile vein arterialisation in the treatment of vasculogenic impotence has usually given satisfactory results. The advantages of this new technique are a simpler anastomosis and the absence of any degenerative atherosclerotic process in the receiving vessel. However, the mechanism of penile revascularisation is difficult to explain. It could be that the new arterial blood flows into the emissary veins of the penis, but control angiography showed no opacification of the corpora cavernosa in the absence of a caverno-venous fistula. While the whole of the deep venous system is visualised when angiography is performed after intracavernous papaverine injection in order to induce an erection, there is no reflux of contrast medium into the corpora cavernosa and at rigidity the penile distension obliterates the venous system between the albuginea and Buck's fascia. Whether flaccid or rigid, therefore, no penile opacification was observed (Figs 1, 2 and 4). It must be noted that control angiography was performed in the immediate follow-up period. Penile retrograde opacification cannot be excluded later if arterial pressure provokes dilatation of the emissary veins.

The glans was always opacified, which explains the appearance of ulceration at this level when arterial pressure is too high (hypervascularisation), as seen in 2 cases. The anastomosis of a circumflex vein or of the DDV extremity into the corpora cavernosa directs the arterial blood into the penis (Fig. 3). This surgical method seems similar to direct penile revascularisation, but the difference lies in the fact that the arterial blood is evenly distributed throughout the entire venous system before entering the corpora and remains subject to the physiological mechanical control of the penile veins. At flaccidity the arterial pressure could be reduced, so avoiding the development of priapism. During erection, compression of the venous system should reduce the arterial flow into the penis. According to Virag *et al.* (1981), who first described this technique, the intracavernous pressure should not exceed 50 mmHg at flaccidity. In our experience, it is between 25 and 30 mmHg and no priapism occurs. However, thrombosis of the anastomosis was observed in 1 patient and the other remains impotent. Corporeal fibrosis secondary to this intracavernous pressure increase could be responsible for these failures. If the clinical results reported in the literature are compared, the greatest improvements are found in patients with venous imcompetence without arterial disease (Virag, 1981; Balko *et al.*, 1986; Bennet *et al.*, 1986). Virag *et al.* (1984) and Austoni (1987) gave no information on the results in relation to the vascular status of their patients. Were the improvements due to the increased resistance distributed diffusely in the venous system or to the ligation of the veins commonly associated with it? We observed no increase in intracavernous pressure after a termino-lateral anastomosis. When a termino-terminal or termino-lateral anastomosis with prox-

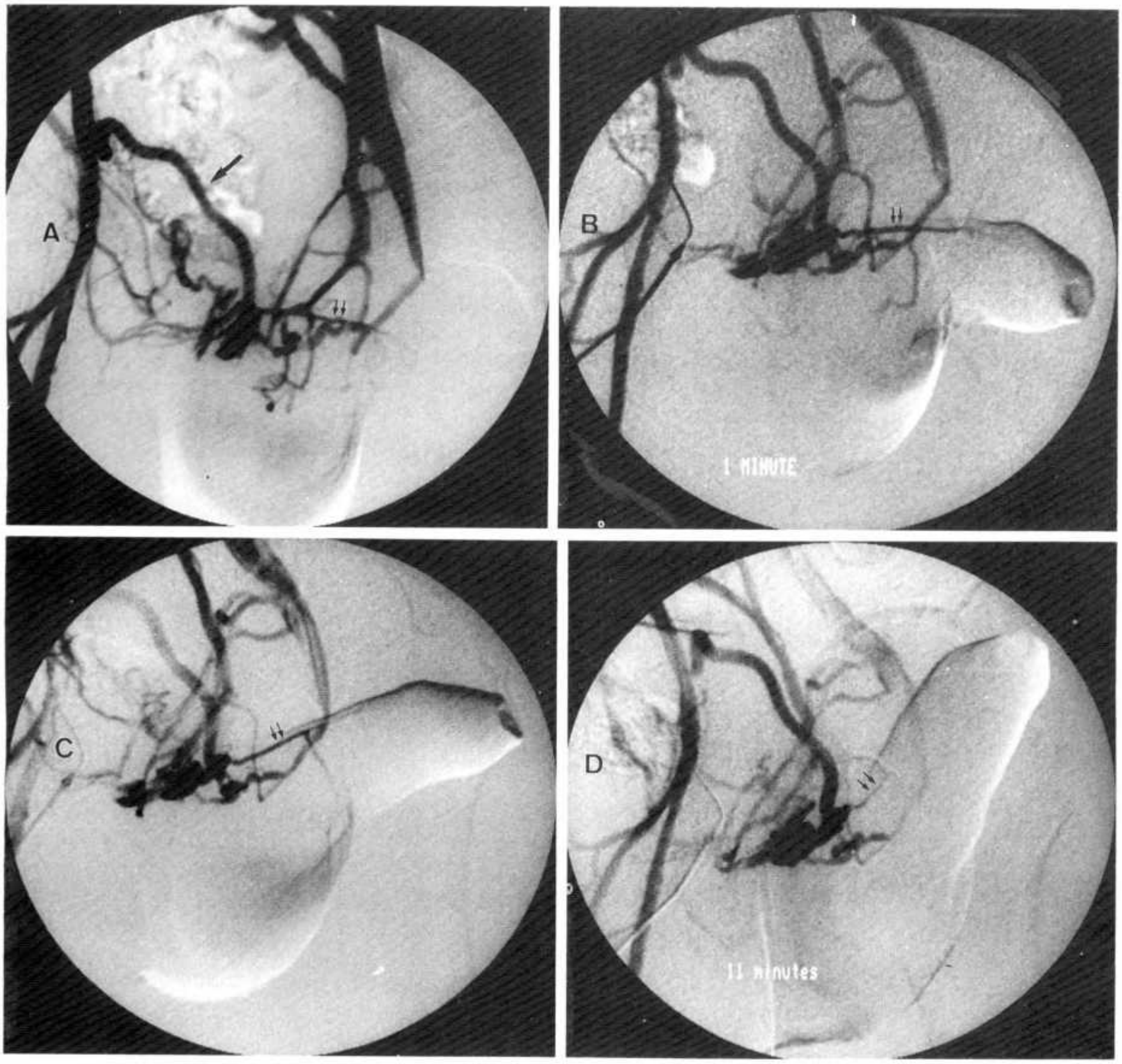

Fig. 4 Digital angiography before and after 60 mg papaverine injected intracavernously. (A) Flaccid state: termino-lateral anastomosis of epigastric artery (↗) into DDV (↗↗). Corpora cavernosa are not opacified. (B) One minute after the injection of papaverine, DDV is still opacified but corpora cavernosa are never opacified. (C) After 3 minutes, the penis becomes tumescent. Decreased opacification of DDV. (D) After 11 minutes, penis appears fully erect. DDV disappears, compressed between Buck's fascia and tunica albuginea.

imal ligation of the DDV was performed, the intracavernous pressure reached values comparable to those observed in patients treated surgically for venous leakage with impaired arterial inflow by simple DDV vein ligation (Wespes and Schulman, 1985).

This type of anastomosis was mainly performed in patients with severe arterial insufficiency to avoid the rapid escape of the arterial flow through the DDV and to allow better revascularisation. Unfortunately, this was not observed. For this reason, a caverno-venous fistula was made in 2 patients. It is likely that when the arterial inflow is retained, the increase in intracavernous pressure is of greater significance, as we found in patients operated upon for venous leakage without arterial lesions (Wespes and Schulman, 1985).

We did not measure the inflow rates necessary to induce an erection during surgery for fear of damaging the anastomosis. Balko *et al.* (1986)

performed a proximal ligation of the deep dorsal vein and noted an obvious decrease in erectile rates, mostly in patients who presented with a pure venous leak. However, they reported that the flow rates did not return to normal until arterialisation was added. It is therefore difficult to explain how arterialisation of the DDV vein works and in our experience the results of this procedure are totally unpredictable. The results reported in the literature seem to be most satisfactory when vascular pathology is limited to a venous leak. The advantages of this technique should be compared to the ligation/resection of the DDV, which is a simpler surgical procedure. The creation of a venous-cavernous fistula improves penile revascularisation when only arterial or mixed lesions exist. However, the results should also be compared with other indirect surgical techniques.

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Priapism in Childhood

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Summary—Priapism is a rare condition in childhood; the majority of reported cases are in boys with sickle cell disease, where conservative management is often appropriate. Our experience with 4 cases, with differing aetiologies, and a review of the literature highlight the need for aggressive therapy when conservative measures fail.

Priapism is an abnormal penile erection which is persistent, painful and generally unassociated with sexual interest. The erection may be intermittent, but can be distinguished by turgidity of the intercommunicating corpora cavernosa in combination with a flaccid corpus spongiosum and glans penis.

The term comes from the name of the Greek god Priapus, the son of Aphrodite, the goddess of sexual love, beauty and feminine fertility. Priapus was regarded as the protector of fertility, agricultural production and good hunting, and was generally held to be responsible for producing beneficial results whatever the occupation being practised.

Several workers have expressed differing views as to the possible mechanism of erection; Bochdalek (1854) and Waldeyer (1899) considered venous occlusion to be the prime factor. Conti (1952), and others this century, have reported findings in favour of tumescence being an increased arterial inflow phenomenon. Recent experiments in animals have found tumescence of the corpora cavernosa to be the result of active relaxation of the sinusoidal spaces, active arteriolar dilatation and active venous outflow constriction acting in combination, rather than a single factor (Lue *et al.*, 1983, 1984).

The understanding of the management of priapism has improved significantly over recent years as a result of the increasing use of intracorporeal agents to produce an artificial erection. For example, it is well recognised that papaverine, a smooth muscle relaxant, and phentolamine, an alpha adrenoreceptor antagonist, are both able to induce erection and priapism when injected into the corpora cavernosa. Agents such as the alpha adrenoreceptor agonist metaraminol have, therefore, been used in treating persistent erection (Brindley, 1983). All of these agents, when used experimentally, have led to the recognition of the existence of 2 subgroups of priapism, 1 due to a low flow rate and the other to an increase in blood flow through the penis (Juenemann *et al.*, 1986). It is this recognition of the pathophysiology and the poor results which dictate aggressive management when conservative treatment fails.

Case reports

Case 1. A 10-year-old boy awoke on the morning of admission with a painful erection. He had a 3-day history of rash over toes and buttocks as well as mouth ulcers. On examination a small number of petechial lesions over his buttocks and toes, palatal ulcers and mild cervical lymphadenopathy were noted. He showed signs consistent with thoracolumbar junction transverse myelitis, lasting only a few hours. His penis was turgid except for the lax corpus spongiosum and glans.

Apart from isolating a urine Echovirus 14, all other investigations were normal, including a full blood examination, lumbar puncture and myelogram.

Local cold application and analgesia were the only treatments administered. The boy's priapism gradually resolved over 48 h. At follow-up his parents reported that he was experiencing normal

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erections and he was neurologically normal when examined.

Case 2. This previously well, 8-year-old boy presented with a 7-day history of moderate priapism. He had only mild penile discomfort and no difficulty in passing urine.

On examination (including rectal examination) he was normal, apart from the finding of priapism. Unlike the other 3 cases his penis was only slightly tender. Red cell morphology, white cell count, pelvic X-ray, coagulation profile, mid-stream urine and a nuclear magnetic resonance scan of his spine were all normal. A positive Coxsackie B_2 titre was obtained, which was lower in the convalescent serum.

Penile aspiration produced a near flaccid penis which then continued to resolve over the following 7 days. His erections have since been normal.

Case 3. Five days after an uneventful appendicectomy this 2-year-old boy presented with signs of a pelvic abscess. He had difficulty in passing urine and had a continuous painful erection with fluctuating levels of turgidity.

He was treated with intravenous antibiotics, phenergan sedation and cold application. The degree of penile turgidity declined over the following 2 days, after which he was discharged. On review his parents reported him to be having normal erections.

Case 4. An 11-year-old boy had been diagnosed as having Fabry's disease 2 years before presenting with a painful, persistent erection of 12 hours' duration. He was not on any medication. He was found to have Fabry's disease (alpha-galactosidase deficiency) on family follow-up and this aspect of his case has been reported in detail by Christodoulou *et al.* (1988).

On examination he was distressed as a result of his penile discomfort but was normal apart from turgid corpora cavernosa. No clinical features of Fabry's disease were found (*i.e.* corneal opacity, angiokeratomas, sweating abnormalities, hypertension, haematuria). Extensive investigation revealed no aetiological factor for his priapism apart from the enzyme deficiency previously noted.

An unsuccessful attempt at cavernosal aspiration was carried out in the casualty department; 24 h after the onset he was given a general anaesthetic, the corpora cavernosa were aspirated and an attempt was made to instil 1 mg of metaraminol, but rapid refilling of the corpora prevented adequate instillation and only partial, temporary detumescence was achieved. Repeat aspiration and urinary catheter insertion were performed 16 h later, with a greater degree of detumescence. At each aspiration, after a small volume of dark blood, bright blood was obtained and the rate of flow into the penis was high; 48 h after onset, further incomplete detumescence was produced by a third aspiration. An Ebbehøj caverno-cavernosa shunt was therefore performed (a narrow blade incision being made in the dorsum of the glans and extended into the corpus cavernosum on each side; the glans was then sutured). Over the following 12 h his erection returned to its initial very turgid state. After a total of 72 h, a second attempt at an Ebbehøj shunt failed to produce complete detumescence and under the same anaesthetic a right caverno-saphenous shunt was carried out. Satisfactory but incomplete detumescence resulted, which resolved slowly.

The patient had an intermittent fever from the time of his admission and was placed on broad spectrum antibiotics. He was discharged 14 days after admission.

A penile Doppler study and ultrasound examination 4 months later showed no fibrosis in the corpora and flow through the saphenous vein shunt. The cavernosal arteries could not be visualised. He had not experienced any subsequent erections.

Discussion

Priapism is now known to be associated with a wide range of aetiologies, may of which are seen in children (Table 1). The increasing use of intracorporeal agents to facilitate artificial erection has meant that adult urologists are dealing with an increasing number of cases. Paediatric patients with priapism remain rare, except where sickle cell anaemia is common (Adeyokunnu *et al.*, 1981).

Because of the wide range of causes it is essential that patients with a painfully prolonged erection have a thorough case history recorded, together with physical examination and appropriate investigations before a diagnosis of idiopathic priapism is confirmed. Our experience suggests the need to add evidence of a recent viral infection to the list of investigations.

It has hitherto been considered that a paediatric patient usually has spontaneous resolution of his priapism and is not helped by intervention. Table 2, however, shows an impotence rate of 14% in a group of 70 patients taken from various published reports and includes only those patients with adequate follow-up: 2% (1/50) were impotent after

Table 1 Aetiology of Paediatric Priapism

- Idiopathic
  - Haematological
    - Sickle cell disease
    - Leukaemia
    - Glucose phosphate isomerase deficiency
    - Abnormal platelet aggregation
    - Hyperfibrinogenaemia
- Local malignancy
  - Infection
    - Pelvic cellulitis
    - Mumps
    - Other viruses
- Perineal trauma
  - Iatrogenic
    - Antihypertensives
    - Haemodialysis
    - Anticoagulants
    - Intravenous fat emulsions
  - Neurological
    - Spinal injury
    - Transverse myelitis
  - Other
    - Diabetes
    - Amyloidosis
    - Fabry's disease

Table 2 Review of Paediatric Management

	Treatment				
	Conservative		*Plus surgery*		
Aetiology	*Potent*	*Impotent*	*Potent*	*Impotent*	*Total*
Sickle cell disease	48	0	3	8	59
Idiopathic	2	0	3	1	6
Other	0	1	4	0	5
Total	50	1	10	9	70

conservative management alone, while almost 50% (9/19) were impotent after surgical intervention. It is our contention that this high impotence rate is due to the delay in carrying out surgery in severe cases because of the view that all paediatric priapism resolves spontaneously. It is notable that those with sickle cell anaemia have a not insignificant impotence rate (14%; 8/59). Two of our patients resolved spontaneously and the third settled following corpora cavernosa aspiration. In the fourth patient, with long-standing underlying pathology (Fabry's disease), detumescence occurred over many days. Although his corpora are not fibrosed on ultrasound, he has not had an erection during an 18-month follow-up period. The presence of flow through the shunt suggests that closure would restore potency. We agree with those who regard priapism as a surgical emergency (Forsberg *et al.*, 1981; Bertram *et al.*, 1985; Kaisary and Smith, 1986). Lue *et al.* (1986) also agree, but maintain that the degree of urgency is greater if the priapism is due to a low-flow rather than a high-flow state.

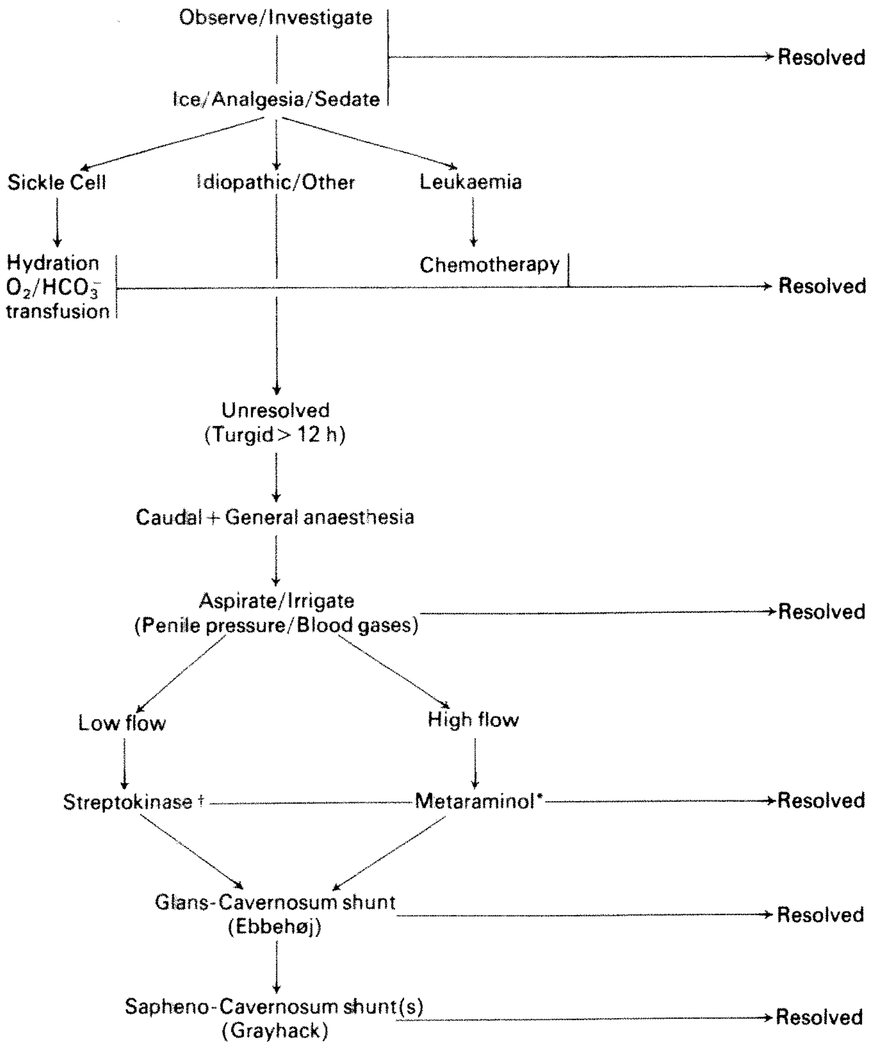
Evaluation of the management of priapism indicates the previous lack of understanding of the pathophysiology of erection. However, some of the earlier techniques are still effective, *e.g.* cold applications (Callaway, 1824), treatment of the aetiology (leukaemia, sickle cell anaemia), sedation and analgesia. On the other hand, systemic anticoagulants, fibrinolytics, hypotensive agents, regional and general anaesthesia are now recognised as being relatively ineffective.

Direct corpora cavernosa aspiration, followed by the instillation of heparin, streptokinase (Gibel, 1985) or alpha receptor antagonists, is now widely advocated, especially the use of metaraminol (Brindley, 1983; Branger *et al.*, 1985).

Several surgical techniques have been used, including incision and drainage (Callaway, 1824) and rectal diathermy. Caverno-spongiosum shunts, advocated by Quackels (1964) and Howe (1969), have been replaced by glans cavernosal shunts created by a narrow blade (Ebbehøj, 1975), Tru-cut needle (Winter, 1976), formal anastomosis described by Al-Ghorab in 1978 (Ercole *et al.*, 1981) and Kerrison rongeur (Winter, 1981). The most popular, more extensive procedure has been the cavernosaphenous shunt developed by Grayhack (1964). Other alternatives include the dorsal vein-cavernosa shunt (Barry, 1976) and embolisation with autologous clot (Wear, 1977; Belgrano, 1984). Neither of these methods has been widely reported. We favour the Ebbehøj glans cavernosal shunt or the Grayhack cavernosaphenous shunt for resistant cases.

Recent work in San Francisco (Lue *et al.*, 1983, 1984; Juenemann *et al.*, 1986) has demonstrated that both high and low flow states can produce prolonged erection, and each produces a different pattern of blood gases within the penis.

The Figure shows the management plan we use for paediatric priapism. It is based on adult and animal models, histopathological changes seen in the penis after 12 hours of a sustained erection (Spycher and Hauri, 1986) and the development of



DOSES: *Proportion of adult dose (1 mg/4 ml saline).
†250,000 units in 50 ml normal saline.

Fig. Management plan for paediatric priapism.

impotence in paediatric patients presenting with a wide range of aetiologies (Table 2).

It is important to recognise that, despite this aggressive therapy, impotence may still occur and parents and children should be forewarned.

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Case Reports

Nodular Peri-orchitis

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Chronic proliferative nodular peri-orchitis or vaginalitis is a rare benign "tumour" which presents with features suggestive of scrotal malignancy.

Case Report

A 34-year-old Indian presented with a 17-year history of a gradually enlarging painless right epididymal swelling. He had no urinary symptoms or significant past medical history. Physical examination was unremarkable apart from the scrotal swelling. The epididymis was firm and irregularly enlarged but the testis felt normal. An ultrasound scan revealed a solid lesion with well defined margins clearly separated from the testis. Haemoglobin, white blood count and chest X-ray were normal.

The swelling was explored through a groin incision; the epididymis was replaced by a hard irregular mass measuring 6 × 2½ × 2 cm with further nodules on the tunica and replacing the hydatid of Morgagni. A radical orchiectomy was performed.

Histological sections revealed calcification and patchy chronic inflammation, consisting predominantly of lymphocytes and plasma cells. The nodule on the tunica was composed of scattered fibroblasts separated by hyalinised fibrous connective tissue. The appearances were typical of nodular peri-orchitis.

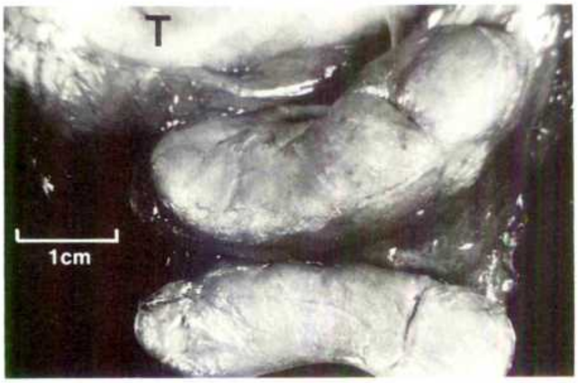

Fig. Operative specimen showing cut surface of the hard mass replacing the epididymis and separate from the testis (T).

Comment

Nodular peri-orchitis is a rare benign reactive fibrous proliferation of the tunica vaginalis. It appears to be a peculiar inflammatory condition of unknown aetiology (Pugh, 1976). Trauma appears to be a precipitating factor in some patients and it usually occurs in 20- to 40-year-old males. The lesion in this patient was typical in appearance, but on occasion nodules may be more widespread throughout the tunica and along the epididymis. The fibromas are often ill-defined, but only occasionally calcified. There are no long-term sequelae and clinical follow-up is not necessary.

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Polyorchidism, Bilateral Double Testis and Unilateral Testicular Torsion

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Polyorchidism is a rare congenital anomaly with only 38 cases reported in the literature (Butz and Croushore, 1978).

Case Report

A 25-year-old male was admitted with an 18-h history of sudden left inguinal pain, oedema and erythema following an energetic movement.

On examination a mass 3.5 cm in diameter was found near the upper pole of the right testis and another mass 4·5 cm in diameter near the external ring of the left inguinal canal. At emergency exploration of the left inguinal region, a 360° torted testis 4.5 cm in diameter was found, together with a normal testis 3 cm in diameter. Orchiectomy was performed for the twisted testis and a biopsy taken from the normal testis. The right scrotal region was also explored. Two testes located side by side were found (Fig.) and biopsies taken for histological examination. Both sides had a single vas deferens.

Comment

At least 6 of the patients with polyorchidism described in the literature had acute or intermittent

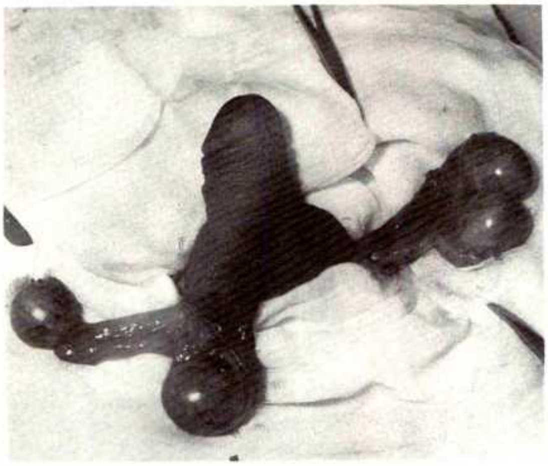

Fig.

torsion and inguinal or lower abdominal pain related to this anomaly (Snow *et al.*, 1985); 30% of patients with this anomaly also have a greater tendency to malignancy than do those with cryptorchidism (Mehan *et al.*, 1976).

Histological examination of the testes of polyorchidic patients usually reveals abnormal tissue structure. In our case, histological examination of the biopsy material showed that both testes in the right scrotum were abnormal, having localised with pericanalicular fibrosis and partial germinal aplasia; the normally sited left testis was histologically normal. The twisted testis in the left scrotum was oedematous, with necrotic seminiferous tubules, and contained no mature sperm.

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Urogenital Myiasis caused by Scuttle Fly Larvae (Diptera: Phoridae)

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A case of urogenital myiasis caused by the larvae of *Megaselia scalaris* is reported. Analysis suggested that the primary cause was partial obstruction of the urinary flow by stone formation.

Most reported cases of urogenital myiasis are caused by the larvae of calyptrate flies (Oldroyd and Smith, 1973). Two cases were caused by larval scuttle flies (*Phoridae*): the first by *Megaselia scalaris* (Priyanond *et al.*, 1973) and the second by *Megaselia kurahashii* (Disney and Kurahashi, 1978; Disney, 1985). The present case originated in St Luke's Hospital, Zomba District, Malawi.

Case Report

A man presented for removal of a urethral stone. He showed a few scales and could easily palpate a 1-cm stone at the base of his penis. The bladder was not palpable. He was given intravenous saline 2000 ml and Lasix, and a good diuresis followed. A total of 20 dead and 3 living dipteran larvae were found in several urine samples. An external urethrotomy was performed. The extracted stone consisted of impacted scales. A bladder stone was also found and removed by cystotomy. The bladder wall was healthy. The patient made an uneventful recovery.

The 6-cm bladder stone consisted of $[Ca_{10}\ (PO_4)\ 6(OH_2)]$ and $[Mg\ NH_4\ PO_4 \cdot 6H_2O]$. The larvae were reared and a male *Megaselia scalaris* obtained.

Comment

Urogenital myiasis is usually associated with patients in poor general health, with poor mobility and ulcerating lesions, but none of these factors applied in the present case.

The classic explanation of urinary myiasis is given by Herms and James (1961): "Infestation is probably usually accomplished at night in warm weather when persons may be sleeping without covering. The flies deposit their eggs around the urethral opening; these hatch in a few hours, and the larvae enter the urethra." All reported incubation periods of the egg in *M. scalaris* seem too long, however, for this hypothesis to be valid; however, eggs laid around the urethral opening would be subjected to temperatures approaching 37°C and how such high temperatures affect the incubation period is not known.

In the present case all larvae were expelled by the forced diuresis, suggesting that obstruction of the urinary flow played a major role. A routine check for obstruction is advised in cases of myiasis.

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Pyrexia of Unknown Origin. An Atypical Presentation of Bladder Carcinoma

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A patient with bladder carcinoma presenting atypically with pyrexia of unknown origin is described.

Case Report

A 63-year-old male smoker, who was known to have a right renal cyst, presented with a 3-week history of backache, nausea and vomiting. He was pyrexial and on rectal examination a hard prostate with a separate mass superior to it was palpable. He had leucocytosis (19.8×10^9/l) and renal impairment (creatinine 757 μmol/l).

Renal ultrasound (Fig.) showed a right 3-cm peripheral mixed echogenic collection at the site of the known cyst with a perinephric collection. The left kidney was hydronephrotic. In an IVU, contrast drained from the right collecting system into the perinephric space. Cystoscopy revealed oedematous irregular urothelium across the bladder base, obscuring the ureteric orifices. Biopsy showed a poorly differentiated transitional cell carcinoma of bladder. He improved temporarily with antibiotics but again became symptomatic.

At operation a thin-walled right renal cyst was deroofed. The perinephric collection was drained. He improved, with his entire urinary output draining from the right loin drain, but subsequently deteriorated and died 4 weeks later.

Comment

Bilateral ureteric obstruction from the bladder carcinoma led to bilateral hydronephrosis and caused rupture of the right calices into the right renal cyst and rupture of the cyst into the perinephric space.

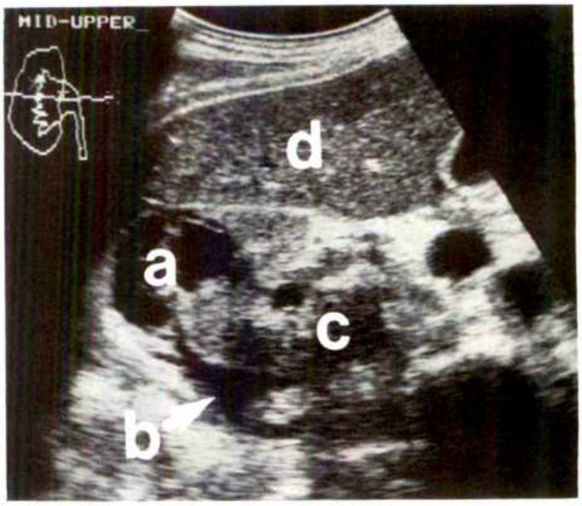

Fig. Ultrasound showing the infected right renal cyst and perinephric collection. a: peripheral infected cyst. b: perinephric collection. c: right kidney. d: liver.

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Pelviureteric Junction Obstruction Secondary to Renal Pelvic Incarceration in a Congenital Diaphragmatic Hernia

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Congenital diaphragmatic hernia is an uncommon condition which usually presents with severe respiratory distress in the neonatal period. Occasionally the defect becomes manifest with chronic symptoms later in childhood or adult life.

We present what we believe to be the first reported case of hydronephrosis secondary to pelviureteric junction obstruction in a congenital, right-sided, posterolateral (Bochdalek) diaphragmatic hernia.

Case Report

A 75-year-old man presented with right hypochondrial pain, nausea and vomiting. He gave a 12-month history

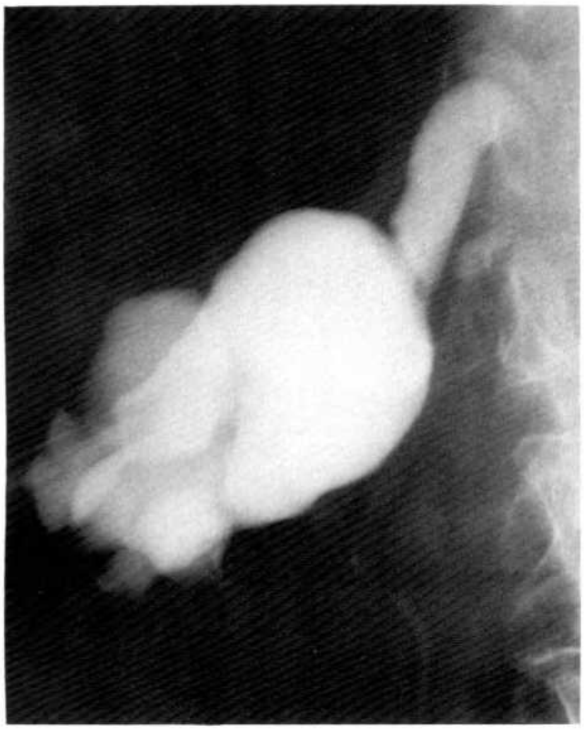

Fig.

of episodes of less severe pain, provoked by drinking beer. He also had constant dyspepsia and chronic obstructive airways disease. He was apyrexial but tender in the right hypochondrium. Ultrasonography, intravenous urography and antegrade pyelography (Fig.) showed a high, dilated right renal pelvis and CT scanning confirmed that the pelviureteric junction was above the diaphragm. Diuresis renography demonstrated an obstructed right kidney.

At laparotomy the right renal pelvis was traced into a posterolateral diaphragmatic hernia. A side-to-side pyeloureterotomy was performed with splintage and nephrostomy drainage. Immediately post-operatively his symptoms were relieved and 2 years later he remains well. Post-operative renography shows a non-obstructed kidney.

Comment

While rare in adults, congenital diaphragmatic hernia is important in the differential diagnosis of obscure abdominal or intra-thoracic symptoms. Retroperitoneal structures such as pancreas and spleen have been reported in such defects but the presence of bowel is more usual (Kirkland, 1959; Ahrend and Thompson, 1971; Ellis, 1986).

The passage of viscera into the chest may be provoked by mechanical factors which raise intra-abdominal pressure. In our patient, coughing associated with chronic obstructive airways disease was probably contributory.

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Large Scrotal Haematoma Treated with Medicinal Leeches

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Case Report

An 81-year-old male developed a large scrotal haematoma following surgery for bilateral hydroceles and epididymal cysts performed through transverse scrotal incisions; 200 ml of blood were surgically evacuated, but the scrotum and surrounding tissues remained tense with haematoma and oedema causing considerable discomfort.

Medicinal leeches were applied to the scrotum until engorged with blood, when they released their suckers (approximately 20 min). The leeches were then placed in 6% sodium chloride solution for 2 min, where they regurgitated the ingested blood. They were then replaced in their individual tanks containing rainwater (Braidwood, 1987).

The process was repeated using 6 leeches daily over 6 days and resulted in considerable reduction of the swelling and symptomatic relief.

Comment

Medicinal leeches have been used extensively in plastic surgery to help preserve grafts when venous drainage remains inadequate. Rao *et al.* (1985) described 7 such cases, including 1 involving the peno-scrotal area. Due to the lax nature of scrotal skin, haematomas can be a considerable problem. Moloney (1975) reported a haematoma rate of at least 17% following surgery for hydroceles and epididymal cysts. We suggest that the prompt use of medicinal leeches can be of great benefit in reducing swelling for the symptomatic relief of large scrotal haematomas.

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Giant Urethral Calculus

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Case Report

An 85-year-old man with a history of chronic bronchitis, atrial fibrillation and pulmonary tuberculosis, was seen in the casualty department with a hip fracture. He said that during military service, 65 years earlier, a doctor had tried unsuccessfully to extract a calculus from the urethra. Since then he had urinated with difficulty and noted a mobile mass in the perineum which he moved laterally himself to pass urine.

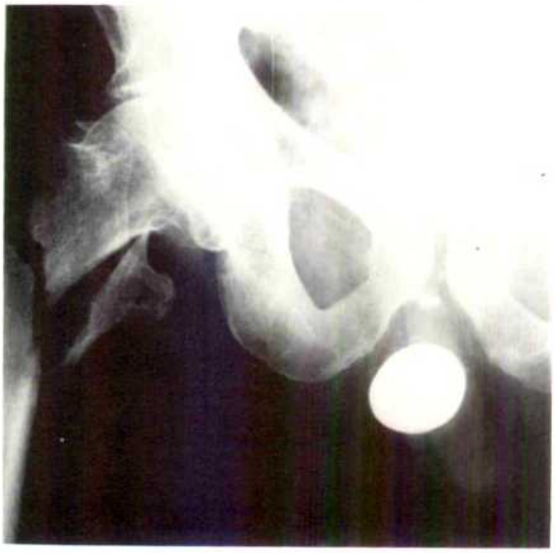

Fig. 1

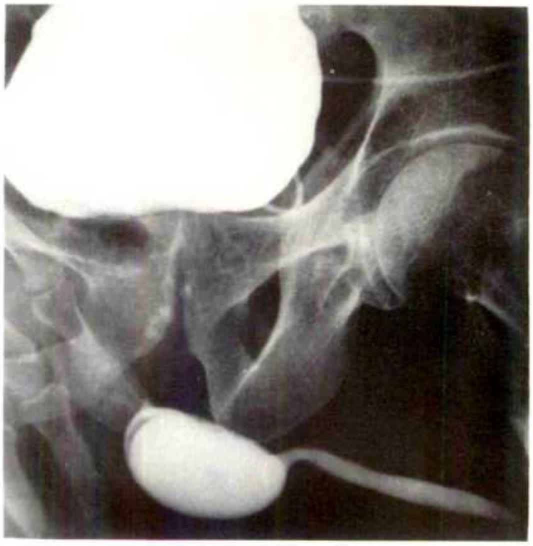

Fig. 2

On examination a hard, mobile tumour was felt in the perineum. It blocked the passage of a vesical catheter and obliged us to insert a suprapubic cystostomy. X-ray showed a fracture of the right hip and a stone measuring 4.5 × 3.5 cm under the pubis (Fig. 1). IVU revealed normal kidneys but the urinary bladder was hypertrophied. Retrograde urethrography showed a urethral stone measuring 6 × 3 cm at the bulbomembranous urethra (Fig. 2). In view of his poor general condition the patient refused operation and has retained the suprapubic cystostomy.

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Paraneoplastic Hypercalcaemia in Association with Schistosomal Bladder Cancer

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Bladder cancer is rarely complicated by bone metastases. Therefore, hypercalcaemia discovered in the course of such a cancer is likely to be due to secretion of some humoral factor by the tumour.

Table Metabolic Investigations

	Reference intervals	*Patient*
S: Total calcium (mmol/l)	2.17–2.57	3.52
S: Ionised calcium (mmol/l)	1.15–1.35	2.04
U: Calcium (mmol/mmol creat)	0.03–0.48	0.95
S: Phosphorus (mmol/l)	0.77–1.36	0.90
Tm PO_4/GFR	0.77–1.45	0.80
U: cAMP (μM/mmol creat)	0.25–0.59	1.15
Secreted cAMP (nmol/100 ml GFR)	0.52–2.00	4.37
S: IPTH (1–84) (pg/ml)		0
S: 25 (OH) D3 (nmol/l)	14–96	9.5
S: 1.25 (OH) 2 D3 (pg/ml)	26–48	50

S = Serum. U = Urinary.

Case Report

A 36-year-old black African woman from Mali passed bloody urine during the fifth month of a fifth pregnancy. Cystoscopy revealed a tumour and schistosomiasis. The tumour invaded the pelvis. Histological examination revealed squamous cell carcinoma and active schistosomiasis. A search for metastases (including bone radiographs) was negative. The discovery of hypercalcaemia prompted metabolic investigations which are summarised in the Table. They were interpreted as showing "paraneoplastic" secretion of a substance which was not immunoreactive PTH, but retained the effect of inducing cyclic AMP secretion by the renal tubule. The persistence of normal to high calcitriol levels was ascribed to pregnancy and possibly contributed to increasing the degree of hypercalcaemia. The patient refused any treatment and died shortly thereafter.

Comment

Paraneoplastic hypercalcaemia has been reported in 17 other cases of bladder cancer and seems to entail an unfavourable short-term prognosis (Notman *et al.*, 1979; Michel *et al.*, 1984; Mundy *et al.*, 1984; Dauge *et al.*, 1985; Ralston, 1987). In 3 cases hypercalcaemia subsided after surgery. In only 3 cases were metabolic investigations undertaken; in 2, nephrogenous cAMP was elevated; in 1 case the iPTH blood levels were high and in the other they were normal; the third patient showed normal iPTH levels and low cAMP secretion. Paraneoplastic hypercalcaemia of bladder cancer, as in other types of tumours, might be due to the secretion of various substances which are different from PTH.

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Point of Technique

Submeatal Injection of Polytetrafluoroethylene Paste for the Endoscopic Treatment of Vesicoureteric Reflux in Adults

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Summary—The injection of submeatal Teflon paste is often used for the treatment of paediatric vesicoureteric reflux (VUR). We present our results using this treatment in 7 adults and 1 female child; 11 ureters were injected with a 73% success rate. The simplicity of the procedure and the encouraging results make this a desirable treatment for adult VUR.

The various surgical procedures to cure vesicoureteric reflux aim to prevent reflux and to protect the kidney from the waterhammer effect of reflux. Adult reflux has received less attention than paediatric VUR. The exact incidence of adult reflux is unknown but an incidence of 23% in patients with chronic pyelonephritis and chronic non-obstructive urinary tract infection has been reported (Senoh *et al.*, 1977).

Until 1972, surgery was reserved for patients in whom conservative treatment was unsatisfactory. Many authors found the results of conservative treatment disappointing and reported that anti-reflux operations in adults produced excellent results (De Sy *et al.*, 1978).

Since Matouschek (1981) reported his experience with polytetrafluoroethylene (Teflon) paste injections for the treatment of VUR this procedure has been used in children (O'Donnell and Puri, 1986; Schulman, 1986). We report our experience with the treatment of 11 refluxing ureters in 7 adults and one 7-year-old girl.

Patients and Methods

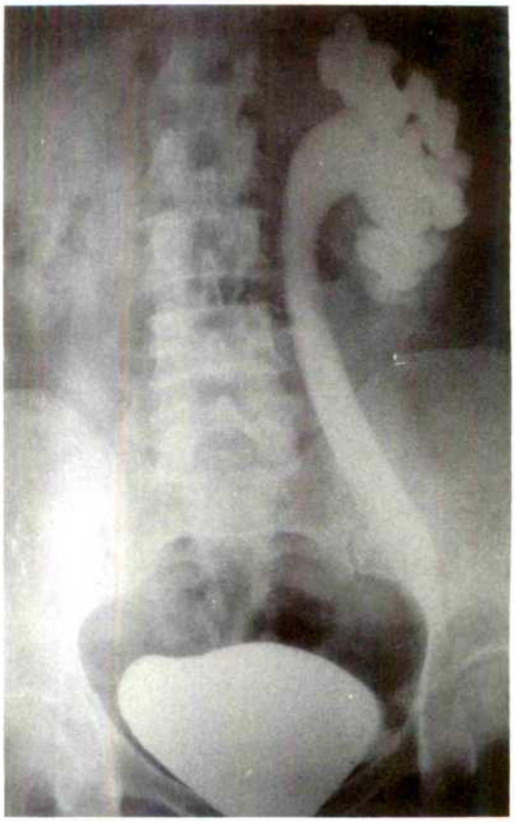

Fig. 1 Left vesicoureteric reflux after unsuccessful ureteric reimplantation due to gynaecological accident.

In 5 patients the reflux was secondary to previous surgical procedures: after transurethral resection of bladder tumours, after partial cystectomy without ureteric reimplantation performed 10 years previously, after a ureteric reimplantation due to a gynaecological accident (Fig. 1), after transurethral unroofing of a ureterocele and after a bilateral reimplantation done 30 years earlier for reasons unknown to the patient. In 2 cases the cause was chronic urinary tract infection and in 1 case (the 7-year-old girl) a neuropathic bladder (Fig. 2).

All of the patients had a cystoscopic examination and voiding cystography (either with contrast or with radioisotope materials that revealed the reflux), intravenous urography, urine culture and renal function tests.

Technique

The procedure was performed under spinal anaesthesia, except in 1 patient who had topical anaesthesia of the urethra.

Injection of the paste is done using a 1 ml syringe filled with Teflon paste and put into a special pistol developed by Storz. A 9 F polyethylene catheter ending with a needle initially filled with the paste is guided through a 23.5 F cystoscope. The needle is inserted under the mucosa, about 0.5 cm below the ureteric orifice at 6 o'clock and advanced 1 cm

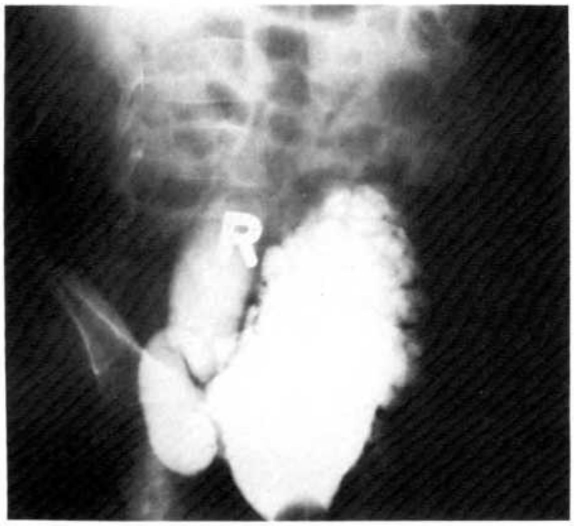

Fig. 2 Cystogram of same patient showing reflux secondary to neuropathic bladder to the right ureter.

alongside the intramural part of the ureter; 1 ml of Teflon paste is injected as the needle is withdrawn. If the ureteric orifice is small, a single submeatal injection at 6 o'clock is sufficient. If the orifice is wide, 2 further injections of 0.5 ml at 3 and 9 o'clock help to reduce its size (Fig. 3). A cystogram is performed on the operating table to assess the result. In our first 3 cases a ureteric catheter was inserted before the injection to prevent complete occlusion of the orifice. Later we only inserted a 5 F catheter for 24 to 48 h after the injection to prevent renal colic. However, we could not insert catheters into 2 ureters and the patients did not develop obstructive symptoms. A bladder catheter is left for 48 h to prevent detrusor contractions that may expel the paste through the injection hole and a second cystogram is done before the bladder catheter is removed.

Results

The results of treatment are summarised in the Table. In 5 ureters each orifice was injected in one sitting; in 3 ureters a second injection was needed and 3 others required a third injection. Ureters that were injected more than once showed a downgrading of reflux in each consecutive cystogram. The procedures were carried out under antibiotic cover. No patient developed fever or renal colic but suprapubic discomfort lasted for 2 to 4 days. In cases where a second or third sitting was needed, the incompletely treated reflux was found in the second cystogram performed before catheter removal. An IVU, an ascending and voiding cystogram, urine cultures and renal function tests were done 3 months after discharge and were compared with the pre-treatment ones. Cystograms and IVU or renograms were repeated after 6 months. No patient showed evidence of obstruction at the vesicoureteric junction. No deterioration in renal function was observed when both sides were injected. The overall cure rate was 73% and the period of follow-up was 6 to 15 months.

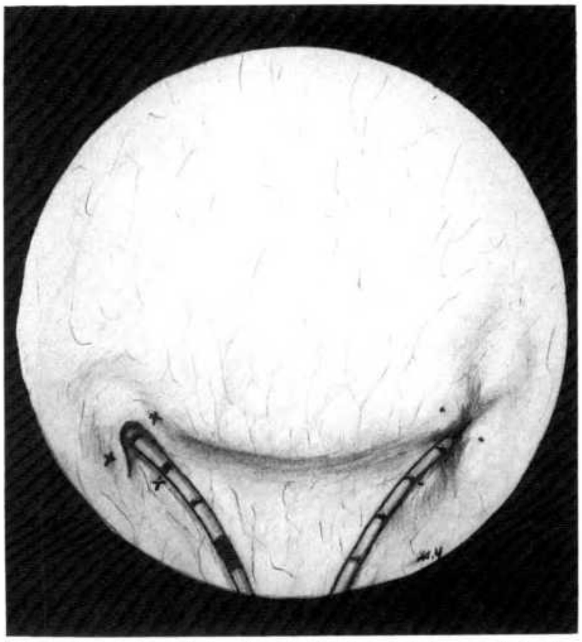

Fig. 3 Ureteric catheters inserted before injection. x: Injection sites at 3, 6, 9 o'clock. •: Injections completed.

Teflon paste is an inert material. The particles of Teflon are suspended in polyethylene-glycol. When injected, the paste causes a foreign body reaction at the injection site and a fibrous capsule develops around the paste (Harris and Hawk, 1969). However, this reaction causes neither sclerosis nor subsequent stricture (Politano, 1982). This mass provides a support against which the intravesical ureter can anchor and compress.

Since 1964, more than 700 patients treated with Teflon paste injections have been reported in the literature (Politano, 1982; O'Donnell and Puri, 1986). None of the reports described a case of Teflon embolisation. However, Teflon particles were found in regional lymph nodes in 1 patient whose death was unrelated to the injection (Vorstman *et al.*, 1985). Malizia *et al.* (1984) reported distant migration of Teflon particles injected

Table Results of Treatment

Patient No.	*Age (years)*	*Sex*	*Side*	*Grade of reflux*	*Cause*	*Symptoms*	*Previous treatment*	*Number of sittings*	*Urine*	*Follow-up (months)*	*Results*
1	49	M	Rt + Lt	4 + 4	Unsuccessful bilat. ureteric reimplantation 30 years ago	Chronic UTI, mild renal failure	Antibiotics, diet	3 + 3	Infected	15	Failure
2	62	F	Rt + Lt	3 + 4	Unknown	Chronic UTI, hypertension	Antibiotics, antihypertensives	1 + 2	Sterile after second sitting	11 Rt 6 Lt	Success
3	49	F	Lt	4	Reimplantation during gynaecological surgery	Chronic UTI	Antibiotics	1	Sterile	12	Success
4	64	F	Rt	4	Transurethral resection of ureterocele	—	—	2	Sterile	15	Success
5	7	F	Rt	4	Neuropathic bladder	Incontinence, chronic UTI	Antibiotics, anticholinergics	1	Sterile under antibiotics	14	Success
6	47	F	Rt	2–3	Partial cystectomy without reimplantation	Chronic UTI, flank pains	Antibiotics	1	Sterile	9	Success
7	54	F	Rt + Lt	3 + 3	Chronic UTI	Chronic UTI, hypertension	Antibiotics	2 + 1	Sterile	9	Success
8	70	M	Lt	3	TUR of intramural ureter for TCC	—	—	3	Sterile	6	Failure

periurethrally in experimental animals. Vascularity and the amount of paste injected may account for this migration.

Whether renal damage is improved or arrested after antireflux procedures is open to discussion (De Sy *et al.*, 1978), but we believe that in patients with progressive renal failure and VUR, an antireflux procedure by surgical or by endoscopic Teflon paste injections is a rational treatment. Our results show that peri-meatal Teflon paste injections are an alternative to open surgical antireflux procedures in adults, especially in non-operated vesicoureteric junctions. This procedure may be performed as a primary treatment or after the failure of surgical treatment and requires hospitalisation for only 2 to 4 days. There is no wound and the patient can resume his regular activities almost immediately after the procedure.

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Notices

British Association of Urological Surgeons

President: R. T. Turner-Warwick, DSc, DM, MCh, FRCP, FRCS, FACS

Annual Meeting. Scarborough. 10–13 July 1990

Abstracts of contributions to be considered as either papers, posters or videos by the Programme Sub-Committee of Council should be submitted on the special forms available from the BAUS Secretariat. Completed forms, which should state clearly whether the submission is a paper, a poster or a video, must be returned to the Honorary Secretary by Friday, 5 January 1990.

Abstracts not on the special forms will NOT be considered.

All correspondence to: M. G. Royle, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

Bard Award

This award, made possible by the generosity of C. R. Bard International Limited, was given for the first time at the Annual Meeting in Bristol in 1979. The award will consist of the sum of £1500 and the Bard Silver Medal. The award will be given for the best essay submitted specifically for consideration for the award by members of the Association (non-members must be sponsored by a Full Member).

Essays should be based on original work on any topic connected with urological surgery, either clinical or experimental. The essay should include a review of the literature and the clinical implications of the work performed. A panel of three adjudicators will be nominated at the February meeting of Council each year. Submissions for the award should be made in triplicate by 1 March to the Honorary Secretary. The winning essay will be read during the Annual Meeting and should not exceed 20 minutes' duration.

Hans Marberger Prize

The Hans Marberger Prize will be awarded for the first time at the meeting of the German Urological Association in Hamburg in 1990. The prize, which will be donated by Karl Storz Ltd, will amount to öS 50,000 and will be awarded biennially for the best paper in the field of reconstructive surgery in urology or endourology. The award may be split.

Papers may be written in either German or English and should be submitted in triplicate to Dr H. Fuchshuber, Adamgasse 15, A-6020 Innsbruck, by 1 March 1990.

A code word should be affixed to each manuscript, which should not bear the author's name. In a separate envelope bearing the code word the following information should be given: author's first name, surname, position, and code word.

British Journal of Urology (1989), **64**, 557–558

Diary

1989

November 20 (SR)	**BAUS Instrument Day—Lasers in Urology** **Royal College of Surgeons, London. Contact BAUS Secretariat. Tel: 01 405 1390**
November 24–25	**International Meeting on Sacral Anterior Root Stimulators—Le Mans. Contact Professor Brindley, The Maudesley Hospital, London. Tel: 01 703 8458**
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1990

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January 8– February 2	**Block 2 Diploma Course, Institute of Urology. Contact Course Secretariat, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01 240 9115**
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January 27– February 3	1990 Winter Urologic Forum Meeting. Steamboat Springs, Colorado, USA. Contact Linda Mace, Staff Assistant, Box 3707, Duke Medical Center, Durham, NC 27710, USA.
March 16	Early Prostatic Cancer—Which Treatment? Newport, Gwent. Contact Mr W. B. Peeling, Department of Urology, St Woolos Hospital, Newport, Gwent NP9 4SZ.
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June 13–16	Ninth Congress of the European Association of Urology. Amsterdam. Contact QLT Convention Services, Keizersgracht 792, 1017 AC Amsterdam, The Netherlands. Tel: 010 31 20261372

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Assessment of the Nephron Segments Involved in Post-obstructive Diuresis in Man, Using Lithium Clearance

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Summary—The phenomena of post-obstructive diuresis and natriuresis have been studied using the lithium clearance technique in 10 patients with high pressure chronic retention. Following relief of obstruction there was a significant increase in both sodium and water excretion. There was a coincident reduction in the fractions of sodium and water reabsorbed in both proximal and distal nephron segments. This study demonstrates for the first time that following relief of chronic obstructive uropathy in man, changes in sodium and water excretion are due to altered handling in both proximal and distal nephron segments.

Post-obstructive diuresis (POD) and natriuresis following the relief of either bilateral ureteric obstruction (Wilson *et al.*, 1951; Bricker *et al.*, 1957; Vaughan and Gillenwater, 1973; Bishop, 1985) or obstruction of a single kidney (Falls and Stacy, 1973) have been recognised for many years. It is now known that increases in sodium and water excretion almost invariably occur following the relief of bilateral obstruction (Jones, 1987; Jones *et al.*, 1988) and these changes are frequently of benefit to the patient, being associated with a reversal of signs of extracellular fluid volume overload (Jones *et al.*, 1987). However, the nephron segments responsible for mediating these changes are less certain. Patients with obstructive uropathy are known to have a defective urinary concentrating mechanism (Berlyne, 1961) and POD is usually resistant to treatment with antidiuretic hormone (Vaughan and Gillenwater, 1973). Consequently the distal tubule and collecting duct have often been considered to be the site of altered sodium and water excretion following relief of obstruction. Conversely, there are case reports suggesting that the quantities of sodium and water (Bricker *et al.*, 1957; Better *et al.*, 1972) and urate (Jones and Nanra, 1983) excreted at this time indicate a contribution to the POD from the proximal tubule. Furthermore, studies of obstructive uropathy in experimental animals have suggested that altered water and electrolyte handling may occur in both proximal and distal nephron segments (Yarger and Buerkert, 1982).

The dearth of information on reabsorption at different nephron sites in human obstructive uropathy has arisen from the lack of a suitable marker of tubular function. It has been proposed that clearance of administered lithium can be used as a measure of fluid delivery from the proximal tubule to the loop of Henle (Thomsen, 1984) and this technique affords the opportunity for an assessment of both proximal and distal tubular function. In the present study, lithium clearance has been used to study the nephron segments involved in altered sodium and water handling during both the obstructed and recovery phases of human chronic obstructive uropathy.

Patients and Methods

Ten men (age range 65–88 years, mean 75) with bilateral ureteric obstruction consequent upon high pressure chronic retention of urine (HPCR) were studied prospectively. Each gave informed consent

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Read at the 44th Annual Meeting of the British Association of Urological Surgeons in Buxton, June 1988

to the investigations and ethical committee approval was obtained. All patients had a tense, painless, palpable bladder and 9 presented with nocturnal enuresis. Urodynamic studies were performed on all patients, confirming the diagnosis on each occasion; 9 underwent intravenous urography (IVU), which showed bilateral hydronephrosis and hydroureter in 8 and ureteric dilatation alone in 1. X-ray was precluded in the remaining patient by a plasma creatinine of 0.44 mmol/l. Mean plasma creatinine during obstruction was 0.17 mmol/l (95% CL 0.11–0.23). All patients had sterile urine.

Drinks containing alcohol and caffeine were forbidden during the study. Before the test period, patients ingested either 500 mg or 250 mg lithium carbonate, depending on body weight and plasma creatinine level, at 22.00 h. The following day a 12-h timed urine collection began at 09.00 h and was completed at 21.00 h. Blood specimens were drawn at the commencement and end of the collection period, placed in tubes containing ammonium heparin and centrifuged to separate the plasma; 1 h later (22.00 h) a further 250 mg lithium carbonate was ingested (all patients regardless of plasma creatinine). The following morning a urethral catheter was inserted and the bladder drained to effect relief of obstruction; 2 h later, a 4-h timed urine collection was commenced and plasma specimens were obtained at the beginning and end of this period. Three or 4 days later, when the POD had subsided (based on clinical grounds), a similar 4-h clearance study was performed after a dose of 500 mg lithium carbonate had been administered at 22.00 h the previous evening. All urine collections were performed under closely supervised urological ward conditions.

Urine and plasma lithium concentrations were determined by atomic absorption spectrophotometry, sodium by flame photometry and creatinine by the jaffe reaction. Clearance of lithium, creatinine and sodium were calculated using standard formulae. The plasma lithium concentration (P_{Li}) for each clearance period was calculated as:

$$P_{Li}=\frac{P_1-P_2}{2.3\log(P_1 \div P_2)}$$

where P_1 = plasma lithium concentration at the beginning of the collection period and P_2 = plasma lithium concentration at the end of the collection period.

Statistical analyses were performed using Student's t test for paired samples. For comparisons of fractional excretion log transformed data were used.

Results

During the period of obstruction, urinary volume and sodium excretion were within normal limits, whilst fractional excretion of water and sodium were raised since creatinine clearance was low (Table 1). Immediately following relief of obstruction (day 2) there was a significant increase in both absolute and fractional water and sodium excretion (Table 1, Fig.), suggesting that there was a marked diuresis and natriuresis resulting from changes in tubular water and sodium handling. Values fell again to baseline levels on day 3, indicating that the diuresis and natriuresis had resolved.

The results of the lithium clearance studies are given in Table 2. Both the absolute volume (C_{Li}) and the fraction of the glomerular filtrate ($C_{Li}-C_{creat}$) escaping reabsorption by the proximal tubules increased following relief of obstruction (day 2) and fell again on day 3 (Fig.). Assessment of the volume reabsorbed in the proximal tubule as $C_{creat}-C_{Li}$ indicated that this was unchanged.

The fraction of the water ($V \div C_{Li}$) and sodium ($C_{Na} \div C_{Li}$) delivered to the loop of Henle and excreted in the final urine increased following relief of obstruction (day 2) and fell again on day 3 (Fig.). Despite these increases in distal nephron fractional excretion, the absolute amount of water ($C_{Li}-V$) and sodium ($[C_{Li}-C_{Na}]P_{Na}$) reabsorbed by distal nephron segments was increased (Table 2). Presum-

Table 1 Absolute Urinary Volume Excretion (V), Sodium Excretion ($U_{Na}V$), Creatinine Clearance (C_{creat}), Fractional Volume Excretion (FEV) and Fractional Sodium Excretion (FE_{Na}) during the Period of Obstruction (day 1), immediately following Relief of Obstruction (day 2) and following Cessation of the Post-obstructive Diuresis (day 3)

	Day 1	*Day 2*	*Day 3*
V	1.08 (0.91–1.26)	*2.73 (1.81–3 63)	*1.06 (0.67–1.45)
$U_{Na}V$	87.0 (61.2–112.8)	*233.1 (171.8–294.4)	†71.2 (48.4–93.6)
C_{creat}	45.9 (24.8–67.0)	54.2 (37.0–71.4)	‡44.8 (38.8–60.2)
FEV	3.13 (1.91–5.13)	*5.09 (2.87–9.04)	†2.50 (1.56–3.98)
FE_{Na}	1.64 (1.10–2.40)	†3.30 (1.90–5.70)	*1.20 (0.80–1.80)

V and C_{creat} are in ml/min. $U_{Na}V$ is in µmol/min. FEV and FE_{Na} are %. Values given are means with 95% confidence limits in parenthesis.
* = $P<0.01$.
† = $P<0.001$.
‡ = $P<0.05$.

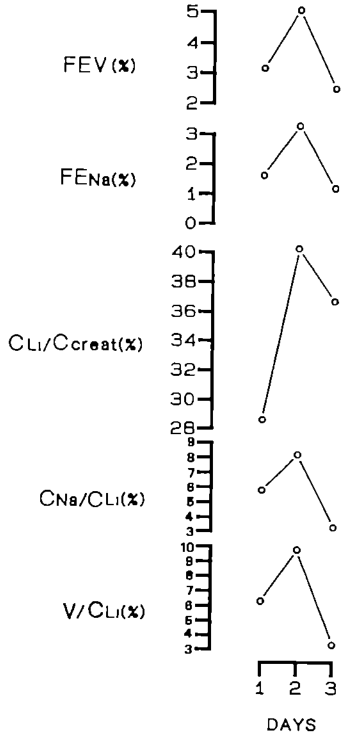

Fig. Fractional sodium and water excretion during obstruction (day 1), immediately following relief of obstruction (day 2) and following cessation of the post-obstructive diuresis (day 3) See Appendix for explanation of derived parameters.

Table 2 Proximal and Distal Sodium and Water Handling during the Period of Obstruction (day 1), immediately following Relief of Obstruction (day 2) and following Cessation of the Post-obstructive Diuresis (day 3).

	Day 1	*Day 2*	*Day 3*
C_{Li}	12.7 (6.05–19.4)	*20 9 (15.4–26.4)	*16 6 (11.3–22.1)
$C_{creat}-C_{Li}$	33.1 (18.1–48 2)	33.3 (20.2–46.3)	28.1 (18.7–37 5)
$C_{Li}\div C_{creat}$	28.6 (22.3–36 7)	*40.2 (32 9–49.0)	36 7 (29.5–46.0)
$C_{Li}-V$	11.6 (5.0–18.3)	§18.2 (12.5–23.9)	15.6 (10.3–20 9)
$V\div C_{Li}$	9.3 (5 7–15 0)	12.7 (7 9–20.2)	*6.3 (4.0–9.9)
$(C_{Li}-C_{Na})P_{Na}$	1707 (780–2635)	*2680 (1892–3468)	2286 (1499–3074)
$C_{Na}\div C_{Li}$	5.8 (4 2–7.9)	‡8 2 (5.2–12.8)	†3.3 (2.3–4.7)

See Appendix for explanation of derived parameters. Values are means with 95% confidence limits in parenthesis. Absolute volumes are in ml/min Absolute distal sodium reabsorption ($[C_{Li}-C_{Na}]P_{Na}$) is in µmol/min. Fractions are expressed as percentages

* = $P<0$ 01.

† = $P<0$ 001.

‡ = $P<0.05$.

§ = $P<0.02$.

ably these changes were a consequence of the increase in delivery of fluid from the proximal tubules which was not fully compensated by altered absorption in distal parts of the nephron. Once again values fell on day 3.

Discussion

This is the first study in man to examine the nephron segments involved in the qualitative and quantitative changes of salt and water excretion following relief of chronic obstructive uropathy. Such studies have been made possible by the recent suggestion that the clearance of administered lithium can provide a measure of fluid delivery from the proximal tubule to the loop of Henle (Thomsen, 1984). However, recent criticisms of the method (Navar and Schafer, 1987) demand that consideration be given to the suitability of the technique when performed under the conditions of the present experiments. It will be realised that traditional free water clearance methods of studying tubule function—requiring fluid loading and many urine collections—cannot be ethically justified in patients with evidence of salt and water retention and impaired excretion ability.

The use of lithium clearance as an assessment of fluid delivery from the proximal tubules is dependent on 2 basic assumptions: (i) lithium is reabsorbed in the proximal tubules to the same extent as sodium and water, and (ii) lithium is not absorbed by the loop of Henle or more distal nephron segments. The available data, reviewed by Thomsen (1984), recent studies in rats (Thomsen and Leyssac, 1986a, b) and man (Atherton *et al.*, 1987) together with theoretical assessment (Skott *et al.*, 1987) suggest that these assumptions are valid unless either salt intake is low or an osmotic diuresis is taking place. However, it must be realised that until there is unequivocal acceptance of this method, due caution must be given to the quantitative interpretation of the current data.

In the present study, dietary salt intake was not controlled but urinary sodium excretion was of a level suggesting that intake was at least moderately high. Additionally, some patients had clinical evidence of salt and water retention (Jones *et al.*, 1987). Thus it seems highly likely that salt intake was sufficient to validate use of the lithium clearance method. An osmotic diuresis may also lead to inaccuracies using this technique. Although it has been suggested that a urea mediated diuresis may be one cause of POD (Maher *et al.*, 1963), we have previously shown that this is extremely rare. The osmotic load almost invariably consists predominantly of electrolytes (Jones, 1987; Jones *et al.*, 1988) and indeed every patient in the present study had a salt diuresis.

Attention must also be drawn to the potential inaccuracies of urine collections during the obstructed phase prior to bladder catheterisation. However, previous work (Jones, 1987; Jones *et al.*, 1988) has shown that urine collections of 12 to 24 h do give an accurate reflection of the urine produced during this time period. Additionally, it is evident that the use of fractional excretion values goes some way to negating this objection as urine volume is used in both the numerator and denominator of the calculations.

The results obtained confirm our previous observations that a natriuresis and diuresis almost invariably occur following relief of bilateral chronic obstructive uropathy (Jones, 1987; Jones *et al.*, 1988). During the obstructed phase (day 1) fractional excretion from the proximal tubule is similar to that observed by Solomon *et al.* (1987) in healthy volunteers on a medium salt diet. Distal tubular fractional excretion prior to relief of obstruction (day 1) is, however, increased above the level that might be expected, suggesting that this nephron segment does contribute to the increased fractional salt and water excretion observed during chronic renal impairment in obstructive uropathy.

Both proximal and distal fractional excretion increase immediately following relief of obstruction (day 2), suggesting that both the proximal and distal nephron segments are involved in the post-obstructive diuresis and natriuresis. Our previous observation that both fractional urate and phosphate excretion increase in conjunction with the salt and water excretion (Jones, 1987; Jones *et al.*, 1988) support the view that the proximal tubule is involved. Bearing in mind the much larger volumes of fluid handled in the proximal tubule, this observation underlines the quantitative importance of this nephron segment.

Following cessation of the POD (day 3), both proximal and distal fractional excretion fall again but their relative contributions to salt and water balance change from that observed during the obstructed state. The significance of this is uncertain, but it may be related to different responses of the obstructed and non-obstructed tubules to hormones responsible for control of sodium and water homeostasis. Clarification of this response awaits further study.

Appendix

The lithium clearance technique is based on the observation that under all but the most avid sodium conserving conditions, lithium is reabsorbed together with sodium and water in the proximal tubule but not in the loop of Henle or distal tubules (Thomsen, 1984). Lithium clearance (C_{Li}) is thus a measure of the volume of proximal tubular fluid delivered to the loop of Henle Therefore the following calculations can be made, using creatinine clearance (C_{creat}) as a measure of the glomerular filtration rate (GFR):

$C_{creat} - C_{Li}$ ≡ volume of tubular fluid reabsorbed in the proximal tubule.

$C_{Li} \div C_{creat}$ ≡ fraction of the glomerular filtrate delivered from the proximal tubule to more distal nephron segments.

$C_{Li} - V$ ≡ volume of tubular fluid reabsorbed in distal nephron segments.

$V \div C_{Li}$ ≡ fraction of the water delivered to distal nephron segments which is excreted in urine.

$(C_{Li} - C_{Na})P_{Na}$ ≡ quantity of sodium reabsorbed in distal nephron segments

$C_{Na} \div C_{Li}$ ≡ fraction of the sodium delivered to distal nephron segments which is excreted in the urine.

Where V = urine volume, P_{Na} = plasma sodium and C_{Na} = clearance of sodium.

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Thermogravimetric Analysis of Urinary Stones

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Summary—Routine thermogravimetric (TG) analysis of 501 upper urinary calculi from the State of Jammu and Kashmir is described. The technique is simple, rapid and quantitative, and the equipment is easily maintained. The technique was found to be helpful in 95.4% of urinary stones and it is suggested that TG analysis may be employed as a technique of first choice in the routine quantitative analysis of all urinary calculi.

Urolithiasis is a common, recurring disorder and may be linked to certain intrinsic and extrinsic factors in the genesis of urinary calculi (Gray *et al.*, 1982). The composition of such calculi is indicative of metabolic disorders (Modlin and Davies, 1981) and thus of clinical significance, requiring the correct identification of their components (Modlin and Davies, 1981; Gray *et al.*, 1982). Many of these stones are of mixed composition (Murphy and Pyrah, 1962; Modlin and Davies, 1981) and consist of a nucleus surrounded by layers, often marked by differences in colour and composition. The nucleus is, however, indicative of the initial metabolic disorder and determines the treatment to be prescribed.

Chemical analytical methods have the disadvantage of requiring large samples and, at best, indicate only the radicals that are present and not the compounds (Rose and Woodfine, 1976).

Physical methods, such as X-ray crystallography (Sutor and Scheidt, 1968) and infra-red spectroscopy (Modlin and Davies, 1981), will identify the compounds but are not fully quantitative (Rose and Woodfine, 1976).

TG analysis of stones, originally suggested by Strates (1966) and further developed by Strates and Georgacopoulou (1969), Berenyi and Liptay (1971) and Rose and Woodfine (1976), is straightforward, rapid and less expensive than infra-red spectroscopy and X-ray crystallography. It is quantitative, free of radiation, and identifies the compounds in a calculus. Rose and Woodfine (1976) demonstrated a close correlation between the results of a chemical quantitative method and TG analysis of urinary calculi.

The present study describes the routine use of TG analysis of 501 surgically removed upper urinary tract calculi.

Materials and Methods

A total of 501 calculi (445 renal and 56 ureteric) were surgically removed from the upper urinary tract between June 1982 and March 1988. The equipment used for TG analysis was a Stanton Redcroft* TG 760 thermobalance consisting of a microbalance, a balance control module and a twin recorder ×1 and ×2 to indicate weight and temperature respectively.

The principle of TG analysis is gradually and linearly to heat in a microbalance a small quantity of crushed calculus to a temperature of 1000°C. As the temperature rises, the powder loses weight and the weight changes occurring at particular temperatures are recorded graphically by the twin recorder. These changes are characteristic of the compounds constituting the calculus and indicate their nature and quantity. Details of the procedure have been described by Rose and Woodfine (1976).

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* Stanton Redcroft Limited, Cooper Mill Lane, London SW17 0BN.

Each calculus was analysed chemically according to the qualitative method of King and Wooton (1982) and some stones were also analysed by the quantitative method of Varley *et al.* (1980).

Interior and exterior portions of 50 calcium oxalate calculi (oxalate content >70%) were subjected to separate TG analysis in order to determine the degree of hydration.

Results

Typical tracings of the various compounds found on TG analysis have been standardised by Rose and Woodfine (1976). TG analysis of 501 upper urinary calculi is shown in the Table.

Of the 50 calcium oxalate stones, the interior and exterior of which were subjected to separate TG analysis, it was found that the content of the interior was 88% monohydrate and 12% dihydrate, whereas the exterior comprised 96% monohydrate and 4% dihydrate.

Discussion

The state of Jammu and Kashmir falls within the "stone belt" of India and upper urinary calculus disease constitutes 35% of the urological workload in this unit; 86.1% of our stones were predominantly calcium oxalate, 81.2% were calcium oxalate monohydrate (whewellite), 4.9% were calcium oxalate dihydrate (weddellite) and 4.9% were a combination of calcium oxalate and calcium phosphate. These figures are higher than those reported in other studies emanating from Western countries (Herring, 1962; Murphy and Pyrah, 1962; Sutor and Wooley, 1972). Of 431 calcium oxalate stones, 339 were found in males and 92 in females. There is a high intake of animal protein in the Kashmir valley and this may be a contributory factor in the high incidence of oxalate stones, although other factors cannot be excluded.

Table Thermogravimetric Analysis for 501 Upper Urinary Calculi

Constituent compounds	*No.*	*%*
Pure calcium oxalate	431	86.1
Mainly whewellite	406	
Mainly weddellite	25	
Calcium oxalate/phosphate	25	4 9
Magnesium ammonium phosphate	14	2.7
Calcium phosphate	10	1.9
Uric acid	6	1.2
Calcium phosphate/magnesium ammonium phosphate	4	0.8
Calcium oxalate/urate	6	1.2
Magnesium ammonium phosphate/calcium phosphate/other traces including urates	1	0.2
Complex mixtures	1	0.2
Failures (unidentifiable)	3	0.6

TG analysis is a satisfactory method for the identification of stones composed of pure calcium oxalate and those composed of both calcium oxalate and calcium phosphate (Rose and Woodfine, 1976); the presence of calcium phosphate may be inferred from the reduced oxalate content, correspondingly increased ash and the absence of positive indications of all other compounds.

Opinions differ as to whether calcium oxalate is laid down as monohydrate, dihydrate or both (Jenson, 1940; Prien and Frondel, 1947; Strates, 1966; Elliott, 1973). TG analysis of 50 oxalate stones revealed that monohydrate comprised 88% of the interior and 96% of the exterior. The corresponding dihydrate content was 12% in the interior and 4% in the exterior. Our findings support the observation of Prien and Frondel (1947) that both monohydrate and dihydrate could be precipitated directly from urine on to the stone surface.

TG analysis of magnesium ammonium phosphate presents special problems since the tracing bears some resemblance to that of brushite. In a brushite stone, however, loss of weight occurs at a higher temperature, over a shorter temperature range and is less than that of magnesium ammonium phosphate. In calculi containing both magnesium ammonium phosphate and calcium phosphate, the precise amounts of these 2 compounds cannot be determined by TG analysis and chemical quantitative analysis is required (Varley *et al.*, 1980). For practical purposes, however, it should be remembered that both magnesium ammonium phosphate and calcium phosphate calculi are infective in origin. Of 14 magnesium ammonium phosphate stones, 13 were found in males and only 1 in a female. The reason for the relatively low incidence of magnesium ammonium phosphate stones in this series is not known.

TG identification of uric acid is characteristic. Of 6 uric acid stones, 5 were anhydrous and 1 was hydrated. The latter gave a TG tracing similar to that of ammonium urate and could be distinguished by excluding the presence of ammonia using the chemical method of Varley *et al.* (1980); 1.2% of our stones were predominantly uric acid, 1.2% uric acid and calcium oxalate and 0.2% were calcium oxalate, calcium phosphate and urate. We found no cystine or xanthine calculi.

Rose and Woodfine (1976) found that TG analysis yielded conclusive information in 63% of their calculi and was less helpful in a further 31%. We found TG analysis to be conclusive in 83.6% of our calculi and less helpful in the 5.8% which were a combination of magnesium ammonium phosphate and calcium phosphate or other complex mixtures. These required corroboration by the chemical method. TG analysis was unsuccessful in stones which were rich in matrix and cholesterol (0.6%).

The time required for a single TG analysis was approximately 35 min and the amount of material required was very low (10 mg). In cases where TG analysis did not yield a complete result, sufficient material was available for corroboration by the chemical method. TG analysis is free of radiation hazards, quantitative and rapid. The equipment is less costly than that required for X-ray crystallography and infra-red spectroscopy and it is suggested that it could be employed routinely for the quantitative analysis of all urinary calculi.

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Does Extracorporeal Shockwave Lithotripsy Cause Hypertension?

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Summary—Several series have suggested that the incidence of hypertension following extracorporeal shockwave lithotripsy (ESWL) may be as high as 8%. In this study, changes in blood pressure and the incidence of hypertension have been observed in 733 patients 12 to 44 months after renal ESWL on the Dornier HM3.

The incidence of hypertension following ESWL was 8.1%. In patients with a pre-ESWL diastolic pressure <90 mmHg, the incidence of those with a diastolic ≥ 100 mm Hg post-operatively was significantly greater than that predicted by historical data. There was no overall change in the mean blood pressure of the group.

The hypertensive risk of ESWL remains unclear. However, blood pressure surveillance should be performed following ESWL and a prospective study is required.

Lingeman and Kulb (1987) were the first to note that there was an increased incidence of hypertension following ESWL. Williams *et al.* (1988) proposed that a possible sequela of renal extracorporeal shockwave lithotripsy was sustained hypertension. In a study of 21 patients attending for follow-up, there were statistically significant increases in both systolic and diastolic blood pressure. Extending this study, 91 patients were reviewed and 7 (8%) were found to have commenced antihypertensive therapy following ESWL. In America the risk of developing hypertension following ESWL is now included as part of the informed consent.

Hypertension following blunt renal trauma is well recognised, but the reported incidence varies widely (Peterson, 1986). Possible mechanisms include development of a "Page-type kidney" which postulates the compression of renal parenchyma as a consequence of fibrosis of perirenal haemorrhage (Peterson and Finlayson, 1986). Alternatively, segmental injury resulting in areas of ischaemia may cause renin release.

Evidence of renal trauma following ESWL is demonstrable by rising serum and urinary enzyme levels and by visualisation of the "injuries" sustained using ultrasound, CT and MR scanning. These changes may persist for more than 6 months (Lingeman *et al.*, 1987; Newman, 1987). Furthermore, Williams *et al.* (1988) have reported a significant reduction in effective renal plasma flow in the 21 patients mentioned above, although this was not confirmed by Chaussy *et al.* (1984).

In view of the possibility that hypertension may occur as a result of ESWL, this preliminary study was performed to investigate the incidence of hypertension following ESWL.

Patients and methods

A retrospective study of 1081 consecutive National Health Service in-patients was performed; all had undergone renal ESWL on the Dornier HM3. Patients with missing records were excluded from the study and pre-operative information was obtained from hospital notes, from which the data were insufficient in 79 cases (7.3%). An explanatory

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letter was sent to 1002 patients, who were requested to visit their family doctor for measurement of their blood pressure and to return this together with details of their current medication.

A total of 800 replies was received (80% response rate). There had been 19 deaths (2.1%) and a further 48 patients had been lost to follow-up. Data were therefore available on 733 patients, of whom 43% were women. The age range was 7 to 80 years (51.8 ± 14.3 years) (mean ± SD) and they received between 110 and 3300 shocks (1429 ± 688 shocks). The follow-up time was from 12 to 44 months (29.1 ± 8.4 months).

Pre-operatively, a stable measurement of blood pressure (BP) was obtained from the patient's BP chart. Post-operatively, blood pressure was assessed by the family doctor, who was asked to repeat any blood pressure measurement that was unexpectedly high, according to their usual practice. Blood pressure was categorised according to the limits shown in the Table. Patients with untreated hypertension following ESWL were reassessed by their family doctor 3 months after the initial follow-up.

Blood pressure data were analysed using the Mann-Whitney U-test and differences between the observed and expected rates of hypertension by the chi-squared test (X^2). Where applicable, groups were compared using Student's *t* test.

Table Limits Used to Define Blood Pressure Categories, with the Number Included and the Mean Age for Each Group

Blood pressure category	*Limits*	*No. (%)*	*Mean age in years (±SD)*
Hypertension	On treatment for hypertension§		
	Systolic>(age+100) mmHg Diastolic>95 mmHg	140 (19.1)	58.1* (±7.4)
Borderline hypertension	Systolic≤(age+100) mmHg Diastolic ≥90 and ≤ 95 mmHg	165 (22.5)	55.3* (±11.8)
Normotension	Systolic≤(age+100) mmHg Diastolic<90 mmHg	428 (54.8)	48.1* (±15.0)

* The ages of patients in the 3 categories varied significantly (Student's unpaired *t* test, $P<0.05$)

§ Patients on diuretics alone not included in the treatment group.

Results

The subdivision of patients according to blood pressure produced groups with significantly different ages (Table). However, there was no difference between groups in the number of shocks received or the length of follow-up. The non-responders did not differ significantly in terms of blood pressure, number of shocks, age, sex or length of follow-up.

Those patients who had died were significantly older than the study group (64.6 ± 8.6 years *vs* 51.8 ± 14.3 years; $P<0.01$). Using mortality statistics to analyse the causes of death, we observed no difference from the norm.

Blood pressure changes following ESWL. No significant overall increase in blood pressure was seen following ESWL for the group as a whole (Fig. 1) or for any of the subgroups. The distribution of diastolic blood pressures before and after ESWL differed significantly (F test, $P<0.05$), although the mean values were the same. Following ESWL, there was skewing of values to the right (*cf.* the observed incidence of post-ESWL hypertension).

The borderline group had a significant fall in mean diastolic pressure (90.3 ± 1.2 to 84.4 ± 9.7 mmHg, $P<0.01$) following ESWL, although the mean post-operative blood pressure in this group was still significantly higher than that of the normotensive group, which remained unchanged.

Hypertension prior to ESWL. There were 140 patients with pre-existing hypertension; 97 (69.2%) were already being treated and no increase was seen in their antihypertensive requirements following ESWL. After ESWL, a further 13 patients (9.2%) had started treatment, 20 (14.4%) remained untreated and 10 (7.2%) had become normotensive.

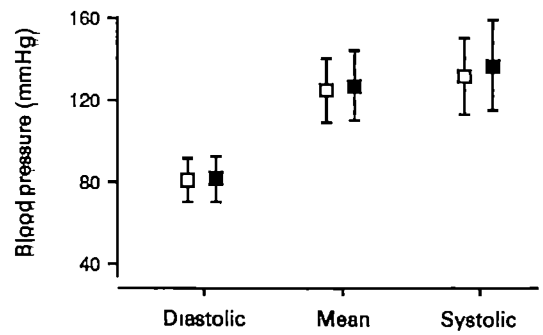

Fig. 1 Diastolic, systolic and mean blood pressure recorded from 733 patients before (□) and 12 to 44 months after (■) ESWL Error bars signify ±1 SD. Mean blood pressure = $\frac{1}{3}$ systolic + diastolic

Hypertension following ESWL. In patients who were initially normotensive or had borderline hypertension, 29 had required treatment for hypertension and 38 were found to have untreated hypertension. However, subsequent reviews of the latter group showed that only 19 had sustained hypertension. The overall incidence of hypertension following ESWL was therefore 8.1% (48/593).

In the normotensive group, 21 patients (4.9%) became hypertensive. Those developing hypertension were significantly older than the remainder of the normotensive group (58.5 ± 11.9 *vs* 47.6 ± 15.0 years, $P < 0.01$) and this age difference was reflected by a higher pre-operative diastolic blood pressure (78.1 ± 3.7 *vs* 74.5 ± 7.5 mmHg, $P < 0.05$).

In the borderline group, 27 patients (16.4%) became hypertensive; they did not differ in age or initial blood pressure from the rest of the group.

Assessment of the incidence of hypertension following ESWL. There is evidence that the risk of developing hypertension is related to an individual's initial blood pressure, age and sex (Miall and Chinn, 1974; Blair *et al.*, 1984). Miall and Chinn (1974), in a longitudinal population study, examined the development of high blood pressure. For groups based on age, sex and initial blood pressure they quoted the number of individuals who, over 4 years, developed a diastolic pressure of 100 mmHg or above.

We have calculated from our pre-operative data the number expected to have developed a diastolic pressure of 100 mmHg or more. The varying length of follow-up has also been taken into account. In those hypertensive patients already on treatment, we obtained their diastolic pressure prior to starting treatment to ensure that they had fulfilled this criterion.

The number of patients from the normotensive group developing a diastolic pressure of 100 mmHg or more was significantly greater than expected (Fig. 2).

Discussion

We were aware at the outset that a retrospective study, without standardisation of the measurement technique and with no direct control population, would hinder us in drawing substantive conclusions, based on the weight of statistical evidence. We were concerned, however, that there may be an association between ESWL and the development of hypertension.

The techniques of measurement of such a variable parameter as blood pressure have been well reviewed by O'Brien *et al.* (1985). Smirk (1944) recognised that a casual blood pressure measurement represented the sum of the stable, basal pressure and the highly variable, supplemental pressure and for an individual the higher the basal the greater the supplemental. The act of measuring blood pressure may, by itself, significantly affect the observed level as seen in white coat hypertension (Pickering *et al.*, 1988).

An individual, therefore, has a variable range of blood pressure (distributed about their mean blood pressure) and a single casual measurement provides an imperfect index of that mean. However, within large groups, the effect of such individual variation, inherent to casual measurements, is reduced and the population mean correlates well with other data, *i.e.* mortality (Pickering, 1968).

The definition of hypertension reflects the increased risk attached to a subpopulation whose mean pressure exceeds the defined limits. As discussed above, some of those defined as hypertensive on casual measurement may, at that time, vary significantly from their mean. In rigorously standardised trials of mild hypertension a significant proportion of the control population will have a reduction in blood pressure (Lancet, 1982; Medical Research Council Working Party, 1985).

Classification of patients on the basis of a single assessment of blood pressure to reflect risk observed from a population mean is, therefore, open to criticism. Only if an individual's mean pressure rises above the accepted limit might he or she be subject to the increased risk—accurate assessment

	Blood Pressure Prior to ESWL	
	Normotensive	Borderline
No expected (Miall and Chinn)	10	26
No observed	18*	24

Fig. 2 The number of normotensive or borderline hypertensive patients expected to have attained a diastolic blood pressure ⩾100 mmHg 12 to 44 months after ESWL, as calculated from the data of Miall and Chinn (1974) compared to the actual number observed. *$X^2 = 6\ 55$, $P < 0.05$

of the mean may only be possible by ambulatory monitoring at home (O'Brien *et al.*, 1985). This would not be practical in a prospective study and inappropriate in a retrospective study.

The significance of small overall changes in mean blood pressure (cf. Lingeman *et al.*, 1989) remains unclear. It is well recognised that an individual's blood pressure increases with age and with improved standardisation of the measurement technique this may simply be an age-related phenomenon. There are very few reports in the literature of longitudinal studies of blood pressure because the above mentioned errors, associated with assessing an individual's blood pressure, will be compounded by the very act of comparison. The problems of analysis of such data and the statistical implications were reviewed by Miall and Chinn (1973).

A recent study of ESWL and hypertension (Lingeman *et al.*, 1989) showed no difference in the incidence of post-ESWL hypertension from a control population; however, the 2 groups may not have been adequately matched. Longitudinal studies (Miall and Chinn, 1974; Blair *et al.*, 1984) have shown that age, sex and the initial blood pressure are the major determinants for developing raised blood pressure—control groups must therefore be matched accordingly. In small studies it may be more appropriate to use matched historical controls.

Given the problems of categorising patients' blood pressure and hence defining those with hypertension, *de novo*, it would be more appropriate in future studies to investigate the incidence of risk events known to be associated with hypertension, *i.e.* stroke, cardiovascular disease, etc.

In this study, although pre-operative measurements may be subject to some degree of systematic error, the large number of observers and sphygmomanometers used post-operatively should result in entirely random errors, reflected by the observed increased variance in blood pressures.

The incidence of hypertension in the study group pre-operatively was similar to that reported in large population surveys (H.D.F.P., 1977). The finding that 8% of patients became hypertensive following ESWL is in remarkable agreement with previous uncontrolled studies (Lingeman and Kulb, 1987; Williams *et al.*, 1988). We have attempted, in all new cases of hypertension, to ensure that the raised pressure was not artefactual. If one looks at the number of new hypertensive patients, *i.e.* those previously normotensive, the incidence of hypertension, *de novo*, following lithotripsy is 2.9% overall.

Following ESWL in normotensive patients, the number with a sustained diastolic pressure above 100 mmHG is significantly higher than that predicted by applying the data of Miall and Chinn (1974). In applying this we have used identical definitions but have assumed that their population was similar to ours.

This assumption may be incorrect as, within a population, stone formers may have a higher diastolic blood pressure than the rest and within a hypertensive group there may be a greater proportion of stone formers (Ljunghall and Hedstrand, 1976). However, we are not aware of any evidence suggesting an increase in blood pressure or an increased incidence of hypertension following treatment of stones by open surgery or endoscopic methods (Marberger *et al.*, 1985; Stackl and Marberger, 1986). Historical data should therefore provide a better matched control group than could be expected by using a small population of stone formers.

The apparent increased incidence of hypertension could have occurred if hypertensive patients were erroneously classified as normotensive in hospital or hypertension was induced by casual measurement on follow-up. We believe the former is unlikely, as a greater proportion of patients had a post-ESWL fall in blood pressure and we have attempted to reduce the latter by reviewing those patients found to be unexpectedly hypertensive following ESWL.

A small age-related increase in blood pressure might have been expected, but the lack of standardisation of the measurement technique may obscure this Sandlow *et al.* (1989), in a similar non-standardised trial, found no change in mean blood pressure and the number with a significant increase in blood pressure was matched by those with a significant fall. Although it is of greater statistical significance that no overall increase in blood pressure was observed, there has been a significant change in the distribution of blood pressures following ESWL, with a skewing to the right.

Although we have shown an increase in the incidence of hypertension and a skewing of blood pressure to the right following ESWL, the significance of late hypertension is still open to question. However, we feel that long-term surveillance of blood pressure is essential after ESWL. A prospective trial is required to answer this important question, which may only be possible by a comparison of the incidence of hypertensive sequelae between 2 matched groups.

An incidence of hypertension after ESWL of 2.9% appears small; however, the normotensive group will have the greater increase in risk. With the large numbers of renal stone patients treated by ESWL world-wide, several thousand patients may have become hypertensive, which would represent a small but important additional risk in the use of ESWL and might influence the future management of upper urinary tract stones.

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Endoballoon Rupture and Stenting for Pelviureteric Junction Obstruction: Technique and Early Results

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Summary—Endoballoon rupture and stenting was performed on 31 patients with pelviureteric junction obstruction. A percutaneous antegrade approach was used in 20 patients, a retrograde technique in 11. Clinical and renographic improvement was seen in 21 patients. Four patients later underwent nephrectomy, all of whom had a GFR of less than 20% in the affected kidney.

Endoballoon rupture is technically undemanding, easier and less invasive than endopyelotomy. In patients with adequate renal function it provides a suitable alternative to pyeloplasty.

Balloon dilatation was first pioneered by Gruntzig and Kumpe (1979) for the treatment of coronary artery obstruction and has now found a wide variety of applications. Advances in endourology have permitted access to the pelviureteric junction (PUJ) and endopyelotomy has now become an accepted alternative to pyeloplasty. The combined use of endourology and balloon rupture is a logical extension of these techniques.

We report the results in 31 patients who underwent endoballoon rupture of PUJ obstruction in 2 urological units (Stirling/Falkirk and Aberdeen).

Patients and Methods

Over the past 2½ years, 18 men and 13 women underwent endoballoon rupture and stenting (ENDOBRST) for obstruction. The age range was 18 to 70 years (mean 33.4). All patients had unequivocal unilateral PUJ obstruction. The diagnosis was established by clinical evaluation, IVU and Tc DPTA or ^{131}I Hippuran renography. Four patients had ipsilateral poor kidney function (<20% on renography); 6 patients had an ipsilateral kidney stone, 5 due to primary PUJ obstruction and 1 coexisting with a PUJ obstruction. Two patients had undergone previous open surgery of the PUJ; 1 patient had had 2 unsuccessful pyeloplasties and the other had an unsuccessful PUJ lysis.

Retrograde ENDOBRST (11 patients)

Under general anaesthesia, cystoscopy was performed and a guide wire and size 8 guiding catheter passed up the ureter and through the narrowed PUJ. The guide wire was removed and the renal pelvis distended with Urografin 38%. The guide wire was then reinserted and the catheter withdrawn. Under fluoroscopy the Olbert balloon 70 cm percutaneous renal access catheter was passed over the guide wire to straddle the PUJ. The balloon was inflated using a pressure inflated handle to a pressure of 180 PSI (9 BAR), reaching a diameter of 10 mm (30F). Waisting of the balloon was seen at the stenosis (Fig. 1A). This disappeared 10 to 20 s after inflation, rupturing the narrowed PUJ (Fig. 1B) and causing extravasation (Fig. 1C). If the waisting did not disappear, the balloon was deflated and then reinflated. This was performed a maximum of 3 times. A size 7 or 8F polyurethane pigtail catheter was then placed to stent the ruptured PUJ for 6 to 8 weeks. A urethral catheter was left in overnight.

Antegrade ENDOBRST (20 patients)

Twenty patients underwent antegrade ENDOBRST, of whom 6 had percutaneous nephrolithotomy at the same time. Under general anaesthesia, cystoscopy was performed and a guide wire passed

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Read at the 45th Annual Meeting of the British Association of Urological Surgeons in St Helier, June 1989

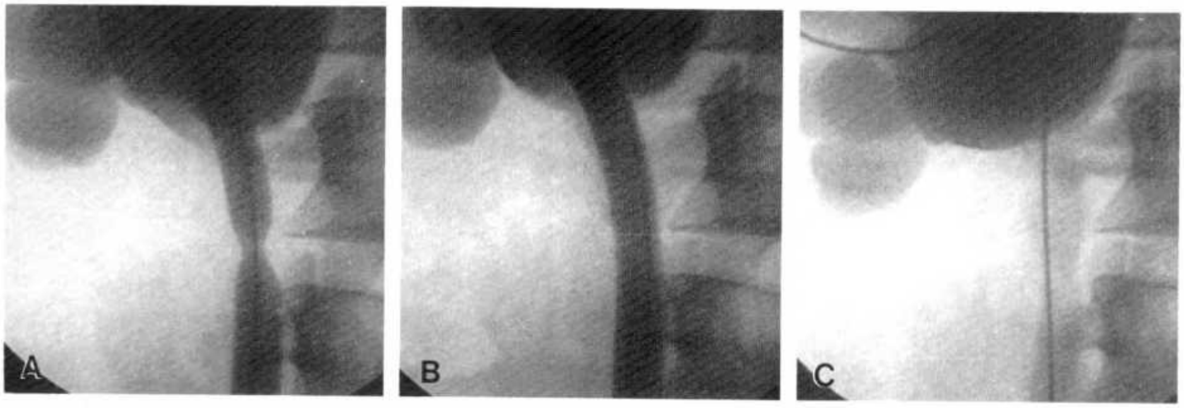

Fig. 1 Inflation of balloon at site of stricture shows waisting (A) which disappears on inflation (B). (C) Extravasation of dye following removal of balloon catheter.

up the ureter and manipulated through the narrowed PUJ. Percutaneous nephrostomy and dilatation were performed in the standard fashion. With a nephroscope the guide wire was extracted through the Amplatz sheath. The Olbert balloon catheter was passed over the guide wire and through the narrowed PUJ. The position of the balloon was confirmed by fluoroscopy. The balloon was then inflated for up to 20 s or until the waisting had disappeared. A size 7 or 8F polyurethane pigtail catheter was then placed over the guide wire and left *in situ* for 6 to 8 weeks. In the early part of the series, 4 patients were treated with size 10F stents.

All patients underwent ^{131}I Hippuran or Tc DPTA diuresis renography 3 months post-operatively. Renography, together with IVU and clinical evaluation, were repeated at regular intervals during follow-up.

Results

Twenty-one patients (68%) had improvement of the PUJ obstruction based on isotope renography and relief of pain (Fig. 2). One patient died of an unrelated cause prior to evaluation. Nine patients had no change, based on diuresis renography; 4 of these patients had a corrected GFR of less than 20% on the affected side and these patients

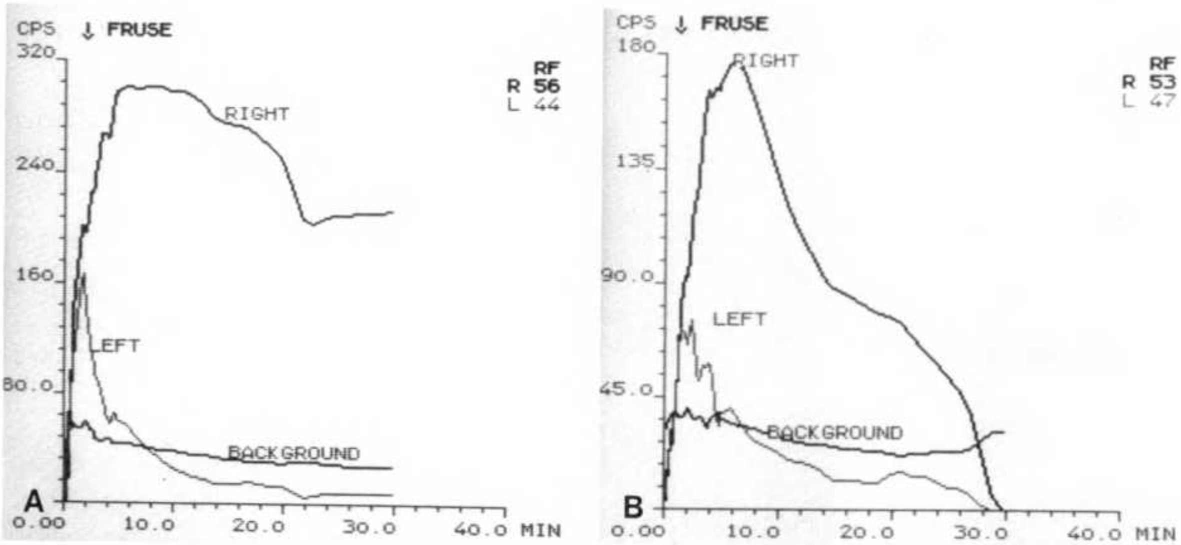

Fig. 2 Diuresis renogram in 30-year-old female. (A) Pre-operative and (B) post-operative renogram demonstrating rapid washout of tracer in response to frusemide.

subsequently underwent nephrectomy. One patient underwent a successful pyeloplasty, 2 are asymptomatic and 2 are awaiting pyeloplasty.

The duration of follow-up was 3 months to 2.5 years (mean 9.9 months). No deterioration in renal function or drainage has been seen during follow-up. Some improvement was seen at 6 months in those whose early renographic improvement was slight.

Complications were small in number and relatively minor (Table). We now use routine antibiotic prophylaxis, which had been omitted in those who developed UTI and septicaemia.

The length of hospital stay averaged 4.3 days (range 2–21). Most patients who underwent retrograde ENDOBRST were discharged the day following the procedure.

Discussion

PUJ obstruction is a common pathological condition which traditionally required open pyeloplasty. Notley and Beaugie (1973) showed that good early results of pyeloplasty were maintained over a prolonged period. The percutaneous incision of stricture at the PUJ was first reported by Whitfield *et al.* (1983), based on the principle of the intubated ureterotomy described by Davis *et al.* (1943). Balloon dilatation of PUJ obstruction was first reported by Kadir *et al.* in 1982. In endopyelotomy, the incision is made in the posterolateral aspect of the stenosed segment to avoid the 20 to 30% of aberrantly placed anterior vessels. With balloon rupture the only requirement is that the balloon straddles the stenosed segment. ENDOBRST is easier and less invasive than endopyelotomy, especially when performed as a retrograde procedure. The operation takes 20 to 30 min and hospitalisation of 2 days is generally adequate.

The antegrade technique has the advantage of allowing the surgeon to perform nephrolithotripsy or biopsy at the same time, while the retrograde technique obviates the need for percutaneous access. During the period of the study, difficulty in negotiating the guide wire through the strictured area occurred in 2 patients, both of whom underwent pyeloplasty.

Four patients had a corrected GFR of less than 20% on the affected side. ENDOBRST was performed in an effort to avoid nephrectomy, but this was unsuccessful. Excluding those with poor renal function, 21 of 26 patients (81%) improved following the procedure. This compares favourably with success rates of 87% for endopyelotomy (Karling *et al.*, 1988). The longest follow-up is 2.5 years and long-term success rates cannot be quoted at present.

Table Complications

Urinoma	1
Stent calcification (kidney stone, ureteric colic)	2
Urinary tract infection	2
Septicaemia	1
Stent migration	2

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Features of Computed Tomography in Hydatid Cysts of the Urinary Tract

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Summary—The features of computed tomography (CT) in 5 patients with hydatid disease of the urinary tract are described. The diagnosis of hydatid disease was based on the demonstration of unilocular or multilocular cysts with well defined walls which enhanced with contrast, which were often calcified and which contained daughter cysts within the large parent cyst. It is difficult to differentiate between a unilocular hydatid cyst without mural calcification and an infected simple renal cyst.

Echinococcosis or cystic hydatid disease is a parasitic infestation that is endemic in some parts of Asia, South America, South Europe, the Near East and Australia. Hydatid disease in Greece (which is among the countries that have a high incidence of echinococcosis) has been found to affect all organs (Golematis, 1978). Within the genitourinary tract the common sites are the kidney and the retrovesical space, although involvement of the kidneys is rare and occurs in only 2 to 3% of all patients with hydatid disease. Although genitourinary involvement is usually renal, prostatic, bladder and epididymal involvement has also been reported (Kirkland, 1966; Diamond *et al.*, 1976).

There is no established medical therapy for hydatid disease and the only treatment is surgical, although it has been suggested that mebendazole may kill the organism (*British Medical Journal*, 1979).

Patients and Methods

Five patients with hydatid cyst of the urinary tract have been examined by CT in this department during the last 6 years; 4 had involvement of the kidney and 1 had involvement of the bladder. The patients (3 women and 2 men) ranged in age from 37 to 68 years. We also present 1 patient with an infected simple renal cyst which was examined by CT and which resembled a unilocular, non-calcified hydatid cyst.

Our patients were either asymptomatic or presented with a flank mass and abdominal pain, or haematuria. In no case had the cyst ruptured into the collecting system of the kidney.

All patients were examined with a Somatom 2 Scanner before and after the intravenous administration of contrast material; 8-mm scans were used at 10-mm intervals from the level of the symphysis pubis up to the diaphragm. Oral contrast was also given prior to the examination. No case of bilateral involvement was encountered. Associated cysts of other organs were present in 2 cases. The final diagnosis was established by surgical exploration in all patients.

Results

The hydatid cysts were located in the renal cortex and were unilocular, multilocular, with or without calcification (Figs 1 and 2). On CT scans, following the intravenous administration of contrast material, there was enhancement of the hydatid cystic wall (Fig. 3), a feature which was also present in the patient with an infected renal cyst (Fig. 4).

In the pelvis, opacification of the bladder

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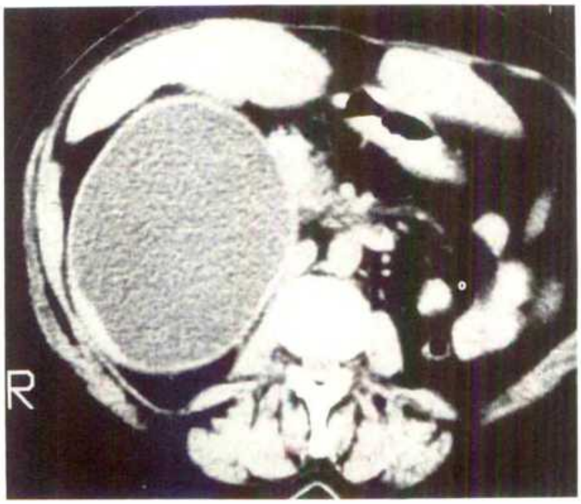

Fig. 1 Unilocular hydatid cyst of the right kidney without calcification.

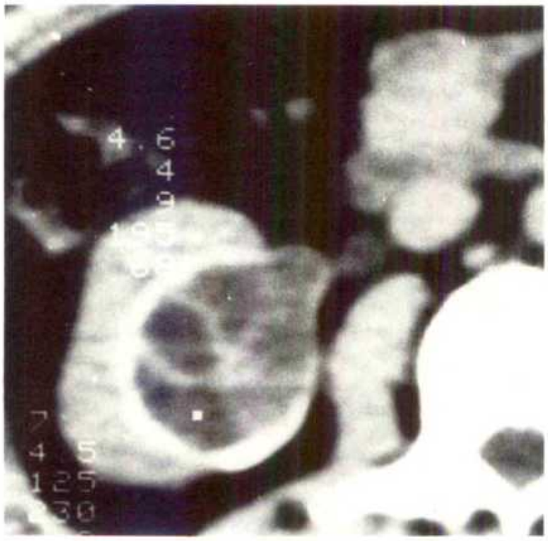

Fig. 2 Multilocular hydatid cyst of the right kidney with calcification.

following intravenous administration of contrast material distinguished the relationships between the hydatid cyst and the surrounding structures (Fig. 5).

The CT findings agreed with the results of conventional studies.

Discussion

Hydatid cysts in man are caused by the larval form of the tapeworm *E. granulosus*, which in its full grown form resides in the intestine of dogs as the definitive host. The larvae in the faeces of the dog contaminate grass and farmland and are ingested by sheep, pigs or man, the intermediate hosts. The larvae hatch, penetrate venules in the wall of the duodenum and are carried by the portal circulation to the liver, which is infected most frequently (70%). The larvae that escape from the liver enter the systemic circulation and may lodge in the lung (25%), the kidney (3%) or in any other organ. The epidemiology and routes of infection in man have been well documented.

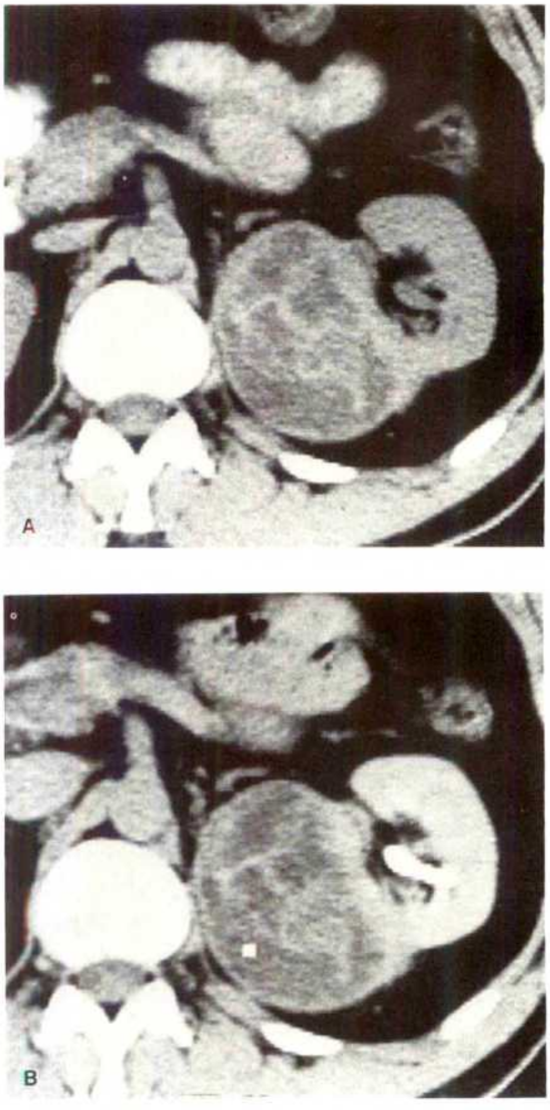

Fig. 3 (A) Non-homogeneous cystic lesion of the left kidney with thick wall. (B) Following intravenous administration of contrast material there is enhancement of the cystic wall.

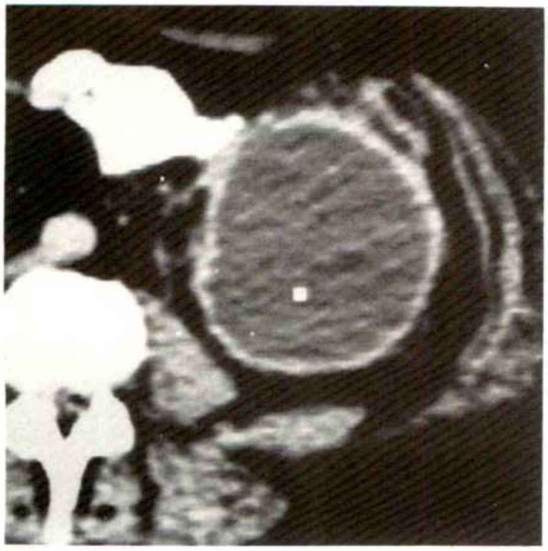

Fig. 4 Cystic lesion of the left kidney with enhancing wall due to infected cyst.

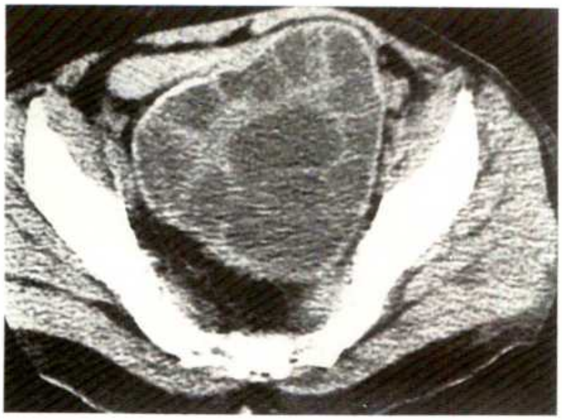

Fig. 5 Hydatid cyst of the pelvis with daughter cysts and small peripheral calcification.

The clinical picture of hydatid cyst of the urinary tract is seldom sufficiently characteristic to suggest the diagnosis. Occasionally, if the cyst ruptures into the collecting system of the kidney, the patient may suffer from renal colic and pass typical "grape-like" material in the urine (Gilsanz *et al.*, 1980).

Skin testing and serological tests are helpful in the diagnosis. The Casoni intradermal skin test yields a true positive rate of 86% and serological tests yield positive titres in 80% of patients. Patients with other helminthic disease, particularly schistosomiasis, may occasionally give false positive Casoni results (Plorde, 1977).

On plain abdominal radiographs, ring-shaped calcifications in the renal or the pelvic area are frequently seen, but are non-specific.

If the cyst ruptures into the collecting system of the kidney, intravenous urography may outline the daughter cysts in the pelvis as irregular masses with or without urinary obstruction. Direct filling of the cyst with contrast medium sometimes occurs, when the daughter cysts may produce filling defects resembling a "bunch of grapes" within the parent cyst, an appearance diagnostic of hydatidosis (Kirkland, 1966).

Nephrotomography and arteriography may help in the diagnosis by demonstrating a thick cyst wall, an avascular mass with a vascular rim, which represents the outer layer of the cyst wall, and by identifying other cysts in extra-urinary organs.

Sonography reveals the lesion as multicystic with mixed echogenicity, mural calcifications and daughter cysts.

Although echinococcal cysts have been punctured without complications (Roylance *et al.*, 1973), diagnostic aspiration is not usually attempted because of the risk of focal dissemination and of serious allergic reactions due to leakage of cyst fluid into the tissue and body cavities (Plorde, 1977).

On CT the appearance of *E. granulosus* in the urinary tract is characteristic (Gonzalez *et al.*, 1979). The demonstration of a unilocular or multilocular cyst, with well defined walls which are frequently calcified, the presence of daughter cysts within a large cyst and increased tissue density of the hydatid membrane which readily enhances after intravenous contrast material, are pathognomonic features of hydatid cyst disease (Kalovidouris *et al.*, 1986).

The CT density of viable daughter cysts is always appreciably lower than that of mother hydatid cysts and this is a useful diagnostic sign. At a relatively early stage of multivesicular hydatid cyst development, the fluid in both mother and daughter cysts is relatively clear, since no appreciable degenerative changes have occurred. However, the density of mother hydatid cyst fluid (15–40 HU) is higher than that of daughter cysts (0–10 HU) (Kalovidouris *et al.*, 1986).

Haemorrhage within or infection of hydatid cysts is accompanied by an increase in the attenuation value of the cyst contents, a change which has also been noted following successful treatment with mebendazole derivatives (Kirkland 1966; Nabizadeh *et al.*, 1983).

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Surveillance of an At Risk Population: Assessment of Postal Urine Cytology

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Summary—The urine postal cytology kit Urotel was assessed against our standard cytological method; 184 patients attending for routine surveillance cystourethroscopy provided free flow urine specimens. The urine cytology was reported blind. Comparison of the 2 tests showed similar specificity but significantly higher sensitivity with the Urotel kit. These kits may have a place in the surveillance of patients at high risk of recurrent tumour or those with carcinoma *in situ*, reducing the frequency of hospital attendance.

Papanicolaou (1947) first established exfoliative urine cytology as a valuable diagnostic aid. Since then it has been used to monitor patients with superficial bladder tumours, upper tract tumours and those with *in situ* and early invasive changes. The specimen for cytological examination must be freshly delivered to the laboratory and this is not always easy.

The purpose of this study was to compare the specificity and sensitivity of Urotel (Weland Medical, Sweden), a postal urine cytology kit, with the standard freshly voided urine cytology in a single blind trial.

Materials and Method

Between January 1987 and January 1988, 184 patients attending for routine review cystoscopy provided a voided urine specimen for cytological examination. If this was the first void of the day, it was discarded to avoid degeneration artefact. Urine was collected prior to cystourethroscopy and processed immediately. The urine was divided, 20 ml being sent for routine urine cytology and the rest prepared for cytology using the Urotel diagnostic kit.

The kit comprises a funnelled plastic sleeve which is divided into 3 compartments by 2 coloured plastic clips (Fig. 1). Urine is poured into the sleeve, having removed the upper clip, mixed with 3 ml 10% trichloroacetic acid and left to sediment overnight (Fig. 1A). The cellular content is isolated

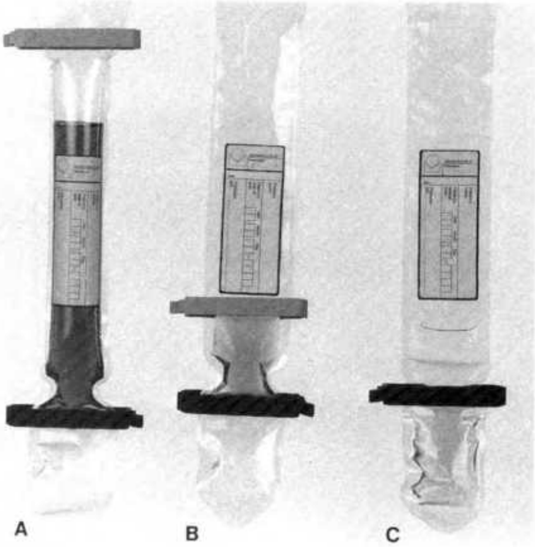

Fig. 1 Preparation of urine specimen with Urotel kit.

Based on a Poster Demonstration at the 44th Annual Meeting of the British Association of Urological Surgeons in Buxton, June 1988

by reapplying the upper clip above the sediment (Fig. 1B). The residual is discarded and the sediment mixed with 10 ml 70% ethanol (fixative) by removing the lower clip. The clip is reapplied (Fig. 1C), the specimen labelled and sealed in a secure snap-top plastic container (Fig. 2). This specimen was then sent for routine cytology.

Both coded control and Urotel specimens were prepared in a similar fashion; 5 ml of urine were aliquoted and centrifuged at 1500 rpm for 5 min. The supernatant was removed and following resuspension the sample was applied to the examination slide using a cytospin technique (1000 rpm for 5 min). Following routine Papanicalaou staining the sample was examined using conventional light microscopy. The samples were examined by one pathologist (M.M.) and reported blind as either positive or negative. The cytology results were then compared with the cystoscopy findings. If the urine cytology was positive and cystourethroscopy negative, the patient was further investigated by intravenous urography.

The paired results were compared statistically using McNemar's test.

Results

The results are shown in the Table.

The specificity of the control (95.5%) and the Urotel (92%) kits was similar, given the small number of discordant pairs. Analysis of patients with superficial tumours showed that the Urotel kit (54%) was significantly more sensitive than the control method (30%) ($P<0.01$). There were insufficient numbers of positive specimens to allow analysis of results in terms of tumour grade and stage. The Urotel specimens were noted to be better preserved than the controls, with fewer degenerate samples.

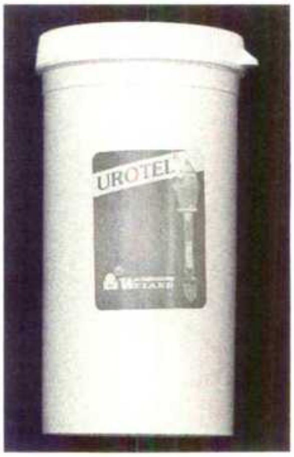

Fig. 2 Specimen ready for dispatch.

Of those patients with negative cystoscopy but positive cytology, 3 had positive cytology on both Urotel and control testing. All 3 patients had negative cystoscopy and negative intravenous urography, but 1 patient developed a ureteric tumour which led to nephroureterectomy 4 months later and a second patient developed invasive bladder tumour 11 months later. The third patient remains tumour-free. Of the 8 patients with 1 sample positive, 6 remain tumour-free.

One patient developed invasive bladder tumour 3 months later, having received a course of intravesical BCG for widespread carcinoma *in situ* 12 months earlier. In January 1989 a second patient was found to have carcinoma *in situ* within the bladder.

Discussion

Although urine cytology is a useful test in high grade tumours, it is accepted that it is difficult to distinguish well differentiated, low grade tumours from normal exfoliated urothelium (Curling *et al.*, 1986). This problem is accentuated by cellular degeneration in the exfoliated cells as a result of prolonged exposure to hypertonic or alkaline urine (Esposti *et al.*, 1970). Freshly voided urine which is

Table Comparison between Cytology Methods and Cystoscopy Findings

	Urotel		
	Negative	*Positive*	*Total*
Negative cystoscopy			
Control			
Negative	102	6	108
Positive	2	3	5
Total	104	9	113
Positive cystoscopy			
Control			
Negative	25	16	41
Positive	2	16	18
Total	27	32	59

No significant difference between control and Urotel. Difference = 3.5% with 95% confidence interval (−2–6.5%).
Comparison false negative rates $P<0.01$ (95% confidence limits 9–30%).

examined immediately is required to optimise the diagnostic benefits of urine cytology.

Our results with the Urotel kit show a similar specificity to that reported by Naslund (1988), but a lower sensitivity. The control test sensitivity was disappointingly low when compared with other series where the average sensitivity rate was 60% (Sarnicki *et al.*, 1971). Despite a significant difference in the sensitivity of the 2 methods tested here, the Urotel kit has a sensitivity of only 54% in spite of better cellular preservation. The lack of sensitivity is probably due to the large number of well differentiated tumours of small overall volume in our patients. Both factors make accurate cytological diagnosis difficult. In Naslund's series, the Urotel kit had a sensitivity of 94% in detecting high grade tumours but failed to detect either of the low grade, well differentiated lesions.

These data show that voided urine, with the addition of a cellular preservative and fixative, can be adequately assessed some time after voiding and the results are at least as good as those of conventional cytology. Both methods have limitations, especially when used to detect well differentiated tumours. However, it is possible to distinguish clinically those patients at high risk of recurrence (Smith *et al.*, 1983) and stricter follow-up regimens have been advocated for these patients. If the tumour is also high grade, the use of Urotel would allow intensive monitoring without the need for the patient to attend hospital so frequently. Another possible use of the technique would be reference cytology for any multicentre trial of therapy for carcinoma *in situ* or other high grade tumours.

The follow-up of patients in the community by means of urine cytology requires the use of preservatives and a safe delivery system. Transport of biological materials in the post has to comply with the Post Office Act 1953 which was amended in August 1987 (James, 1988). The addition of an absorbant material to the plastic specimen box, and wrapping the plastic tube in a sealable plastic bag, would comply with those guidelines.

In conclusion, the use of histological fixatives improves urine cytology and this method of collection and delivery would be useful in monitoring high risk patients in the community, thus obviating frequent hospital visits.

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Transrectal Ultrasound Scanning in Urinary Incontinence: the Effect of the Probe on Urodynamic Parameters

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Summary—A linear array real time transrectal ultrasound technique was used to screen the bladder and urethra of female patients with urinary incontinence during urodynamic investigation. There was no significant difference in any of the urodynamic measurements with or without the probe *in situ*.

Investigation of the incontinent patient includes the objective measurement of urine loss, urine flowmetry and cystometry and is often combined with videocystography to image the dynamic changes of bladder and urethra in response to stress. We have been using a real time linear array transrectal ultrasound technique to study the bladder and urethral relationships in patients with urinary incontinence (Richmond *et al.*, 1986). We have developed computer software to record urodynamic measurements on the ultrasound screen and hence provide similar information to that of videocystourethrography. However, because of concern about the effect of the rectal ultrasound probe on bladder and urethral physiology and consequently urodynamic measurements, this study was devised to evaluate the effect of the transrectal probe on standard urodynamic parameters.

Patients and Methods

We studied 43 female patients who were attending the urodynamic unit. Investigations included history and examination followed by a midstream urine specimen. Urodynamic investigations included a perineal pad weighing test and urine flowmetry with supine and erect medium-fill water cystometry. Intravesical pressure was recorded continuously but readings were taken at 1-min intervals until functional capacity was reached (F3). When pressure changes occurred the maximum value during cystometry was recorded (pMax). A urethral pressure profile (UPP) was recorded using a fluid-filled double lumen Portex catheter. The maximum closure pressure (MCP) and functional length (FL) of the urethra were calculated. A fluid bridge test (FBT) (Sutherst and Brown, 1980) was then performed in the supine and erect positions. The bladder was emptied and the ultrasound probe inserted into the rectum before the urodynamic tests were repeated. We used an Aloka SSD 210 DX portable real time scanner. The diameter of the linear array transrectal probe was 1.5 cm.

Results

Cystometry

Twenty-four patients underwent supine and erect cystometry with and without the probe *in situ*. The diagnosis in each case was the same irrespective of the presence of the probe. Group A comprised 9 patients with genuine stress incontinence (GSI). In Group B were 10 patients with detrusor instability (DI), 2 with combined GSI and DI and 3 with the cystometric characteristics of a small volume, low compliant bladder. The diagnoses conformed to the definitions laid down by the International Continence Society (Bates *et al.*, 1976, 1977, 1981).

There was no statistical change in functional

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bladder capacity and the difference in the maximum pressure rise in cm H_2O did not achieve significance irrespective of the diagnosis or the presence of the ultrasound probe in the rectum.

The 1-min pressure recordings with and without the probe *in situ* were difficult to interpret. Patients with GSI did not show any significant pressure changes during cystometry. However, for patients with DI/poor compliance, although the pressure changes varied from minute to minute, the final diagnosis was the same for each patient (Table 1).

Urethral Testing

A total of 43 patients underwent urethral tests which included UPP and FBT; 15 of these were patients who had undergone full cystometry described earlier. No significant difference was observed in the MCP, FL or FBT measurements with or without the probe *in situ* (Table 2).

Two clinical examples of cystometric traces are presented for comparison (Figs 1 and 2).

Discussion

The effect of anal or perineal stimulation upon urethral and bladder function remains controversial. Denny-Brown and Robertson (1933) found that perineal stimulation led to the inhibition of detrusor contractions in paraplegic patients. Similar results were reported by Parker and Rose (1937). Kock and Pompeius (1963) studied detrusor muscle activity in 25 patients undergoing urological investigation. Using medium-fill water cystometry they observed intermittent bladder pressure waves in 21 patients. Anal digital stimulation inhibited the detrusor contractions in 20 of these patients, but the contractions returned when the finger was removed. It is possible, however, that these were related to rectal smooth muscle contractions rather than the detrusor muscle, since no traces were presented.

Table 1 Statistical Analysis of Intravesical Pressure at 1-minute Intervals, Functional Capacity (F3) and Maximum Intravesical Pressure Recording (pMax)

One-minute pressure readings without probe (A) with probe (B) in situ	*P value (9 patients without DI)*	*P value (15 patients with DI or low compliance)*
A1/B1	1.000	0.813
A2/B2	0.465	0.099
A3/B3	0.402	0.023*
A4/B4	0.249	0.075
A5/B5	0.345	0.600
AF3/BF3	0.116	0.551
ApMAX/BpMAX	1.000	0.551

Student's *t* test *P* values (*$0.01 < P < 0.05$).

Table 2 Statistical Analysis of Urodynamic Results (A) without probe and (B) with probe *in situ*. (Student's *t* test)

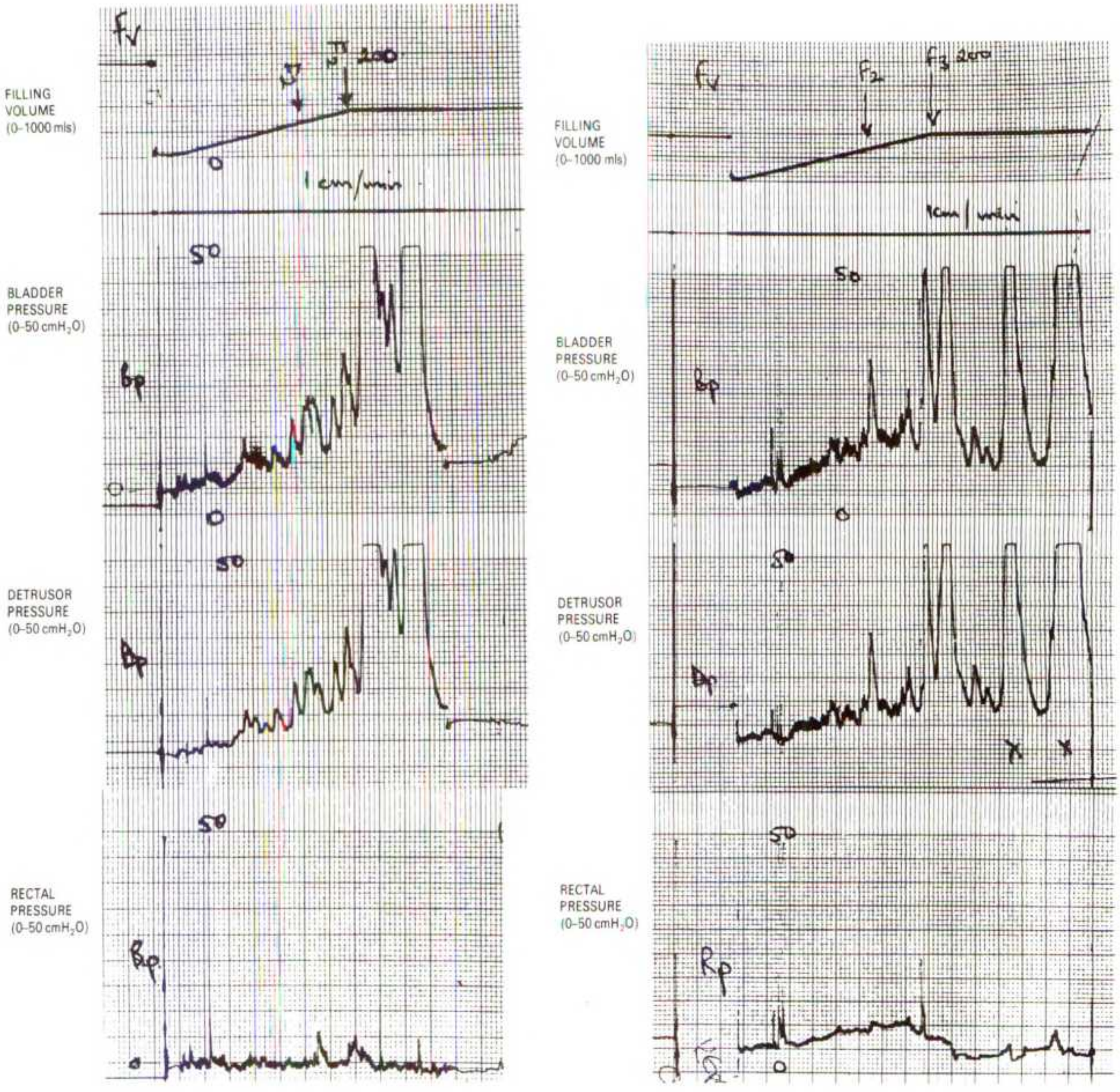
Value	*Mean*	*Standard deviation*	*P*
AMCP (cm H_2O)	76.8	32.2	0.101
BMCP (cm H_2O)	73.7	32.7	
AFL (cm)	3.1	0.6	0.865
BFL (cm)	3.1	0.7	
AFBT (cm)	1.3	0.7	0.421
BFBT (cm)	1.3	0.7	

Other authors have claimed considerable differences between the activity of the anal and urethral sphincters on histological (Gosling and Dixon, 1977), electromyographical (Vereecken *et al.*, 1977) and electrophysiological grounds (Bowen *et al.*, 1976). Vereecken *et al.* (1981) and Koyanogi *et al.* (1982) showed that the levator ani, external anal sphincter and striated urethral sphincter can all contract and relax independently of each other.

In this study no significant differences were observed in any of the urodynamic parameters which are commonly measured. The diagnosis, particularly of patients with detrusor instability, was unchanged.

An attempt was made to screen patients voiding. However, this was successful in only 2 of 6 cases. At present this particular probe is hand held and it was therefore technically difficult to scan the patient. We hope to procure a chair-mounted scanner for further study which will provide a more socially acceptable investigation.

These data would tend to confirm the anatomical and physical studies alluded to earlier which subscribe to the view that the activity and function of the urethral and anal sphincter are dissociated. Transrectal ultrasound scanning does not appear to produce any adverse effects on standard urodynamic investigations and provides an excellent alternative means of imaging the bladder and urethra compared to X-ray cystography. However, the conclusions from this study cannot be extrapolated to all groups of patients and, for example, the findings in patients with spinal cord disease need further study.



A CYSTOMETRY (normal)

B CYSTOMETRY (rectal probe)

Fig. 1 D.W. Age 36. Gravida 4. Symptoms of frequency, nocturia, urgency, stress and urge incontinence with nocturnal enuresis. Pad test 15.9 ml. Urodynamic diagnosis severe detrusor instability. Treatment with oxybutinin.

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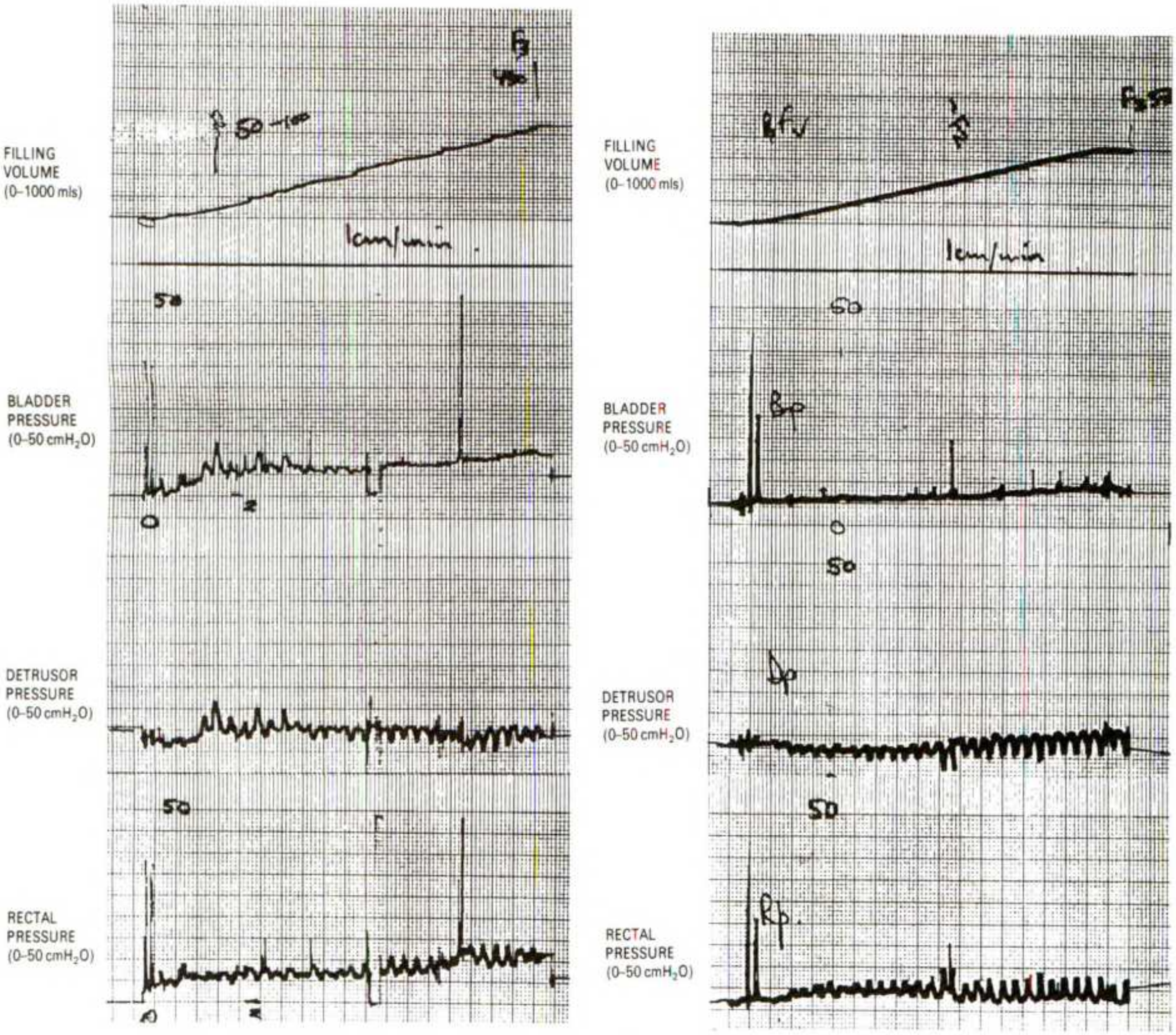

A CYSTOMETRY (normal)

B CYSTOMETRY (rectal probe)

Fig. 2 A.M. Age 22. Gravida 1. Twelve-month history of stress incontinence following childbirth. Pad test 11.3 ml. Normal flowmetry. Cystometry—first desire to void at 100 ml with stable configuration to 430 ml. Fluid bridge test positive at 1 cm. Treatment with physiotherapy. (Note rectal smooth muscle contractions with and without the ultrasound probe *in situ*).

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Factors Determining the Outcome following Implantation of the AMS 800 Artificial Urinary Sphincter

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Summary—Erosion and infection are major complications following implantation of the AMS 800 artificial urinary sphincter. In the present study, 17 patients with this prosthesis were investigated urodynamically. All were continent. Urethral pressure profilometry showed a significantly lower intra-urethral pressure than would have been expected from the pressure installed in the pressure regulating balloon during operation. The maximal urethral pressure was 69.9% of the expected pressure and did not vary significantly in relation to the various balloon pressures. The mean maximal urethral pressure (±SEM) between the cuff when inflated and when deflated was also significantly different, although the absolute difference was small (14.1 cm $H_2O \pm 10.0$). There was good correlation between maximal urethral pressure and urethral leakage pressure as measured by retrograde perfusion sphincterometry. The mean functional urethral length became significantly longer after implantation of the cuff.

A combination of low urethral pressure and increased functional length may help to prevent cuff erosion and maintain continence.

For many patients implantation of the artificial urinary sphincter means the final solution to their otherwise intractable incontinence. Following improvement of the technical aspects of the device and surgical technique, the continence rate became satisfactory and the post-operative complication rate was significantly reduced (Goldwasser *et al.*, 1987). Erosion and chronic subclinical infection, however, still present major problems (Furlow and Barrett, 1985). Blood flow is impeded when local compression of tissue by the cuff becomes too high and erosion results from necrosis of the urethral wall due to insufficient vascularisation. Primary deactivation (Furlow, 1981) and nocturnal deactivation (Goldwasser *et al.*, 1987) tend to relieve the pressure and prevent erosion, but high pressure may be needed to ensure continence. In order to assess the degree of local pressure exerted on urethral tissue by the cuff, we measured the urethral pressure profile in continent patients after implantation of the AMS 800 urinary sphincter prosthesis.

Patients and Methods

Seventeen patients with the AMS 800 prosthesis (American Medical Systems, Minneapolis, USA) were investigated. The time between implantation of the device and urodynamic evaluation varied between 6 and 52 months (mean 25.2). The sphincter was implanted because of a structural lesion of the sphincter mechanism in 13 cases; the remaining 4 patients had a neurogenic disorder (Table 1).

There were 11 male and 6 female patients, ranging in age from 8 to 81 years (mean 63.2). In all female and 2 male patients the cuff was placed around the bladder neck. In the other 9 male patients the cuff was placed around the bulbous urethra. Cuff pressure was installed according to the manufacturer's directions. After pressurisation

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Table 1 Indications for AMS 800 Sphincter Implantation

	Males	*Females*
Structural Defect in Sphincter Mechanism		
TUR prostate	10	—
Radical prostatectomy	1	—
Previous urethral surgery	—	1
Previous anti-stress inc. surgery	—	1
Neurogenic Defect in Sphincter Mechanism		
Myelomeningocele	—	3
Spinal cord injury	—	1
Total	11	6

of the cuff the reservoir was filled with a fixed final volume of 20 ml.

Pressure in the pressure regulating balloon ranged from 51 to 60 cm H_2O in 1 patient, 61 to 70 cm H_2O in 14 and 71 to 80 cm H_2O in 2 patients.

In all cases the device was left deactivated in order to create optimal conditions for tissue regeneration (primary deactivation). After 6 weeks the device was activated.

Urethral pressure profiles were measured by means of an intraluminal microtip pressure transducer. By slowly moving the tip of the transducer from the bladder to the meatus the urethral pressure was measured with the cuff in the closed and again in the open position. The maximal urethral pressure (MUP) and functional urethral length (FUL) were calculated. FUL was defined as the length of the urethra along which the intra-urethral pressure exceed bladder pressure. The Figure shows an example of urethral pressure profiles before and after implantation of the prosthesis.

In order to evaluate whether MUP could be compared with urethral leakage pressure, retrograde perfusion sphincterometry (Leach and Raz, 1983) was performed in all male patients. An 8 F Foley catheter was placed in the anterior part of the urethra, the balloon of the catheter was filled with 2 ml and urethral leakage pressures were determined by the infusion of fluid from a calibrated system above the patient. The pressure at which fluid started to drip into the bladder when the cuff was closed was called the urethral leakage pressure. The procedure was repeated with an open cuff. The urethral leakage pressure was determined by a second investigator who did not know the results of the MUP as measured by the pressure transducer.

Results

All 17 patients were continent, *i.e.* no urinary leakage occurred or only a few drops were lost. No patient showed signs of erosion or infection and satisfactory function of the device was confirmed under fluoroscopic control. Fluid transport from cuff to balloon at the time of pump manipulation was observed and inflate-deflate roentgenograms were obtained.

In all cases the MUP as measured by the pressure transducer with the cuff inflated was compared with the pressure installed during operation. The mean MUP (±SEM) was 45.6 cm $H_2O \pm 7.5$. The mean cuff pressure was 65.6 cm H_2O (Table 2). Thus the mean MUP with the cuff inflated at the time of follow-up was 69.6% of the expected pressure installed during operation. This difference was statistically significant ($P < 0.001$, sign test).

Urethral pressure profiles were also measured with the cuff deflated. The mean MUP measured

Table 2 Urethral Pressure Profile Measurement (n = 17)

	P balloon (cm H_2O)	*No*	*P cuff inflated (cm H_2O)*	*P cuff deflated (cm H_2O)*
	51–60	1	40	20
	61–70	14	46.5	32.3
	71–80	2	42.5	32.5
Mean ± SEM	65.6		45.6 ± 7.5	31.6 ± 14.4
ΔP mean 1			20.0 ± 8.8*	
ΔP mean 2				14.1 ± 10.0*

ΔP mean 1 = P balloon − P cuff inflated
ΔP mean 2 = P cuff inflated − P cuff deflated
* $P < 0.001$

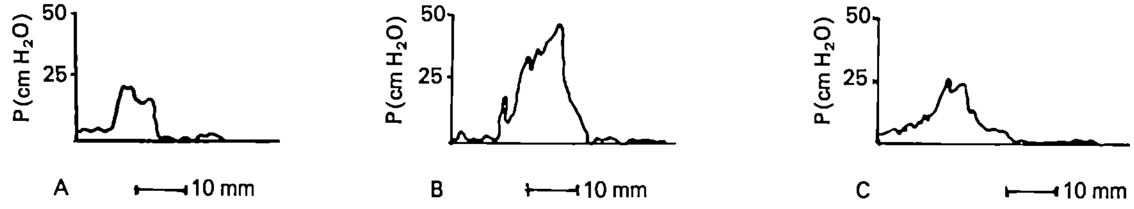

Fig. Urethral pressure profile measured by microtip pressure transducer. (A) After radical prostatectomy and severe incontinence. (B) After implantation of the AMS 800 sphincter. Cuff inflated, 61–70 cm H_2O pressure regulating balloon. (C) Cuff deflated.

with the cuff deflated was 31.6 ± 14.4 cm H_2O. The mean difference in MUP between the inflated and deflated cuff was 14.1 cm $H_2O \pm 10.0$. The mean pressure difference was 30.8% and was statistically significant ($P < 0.001$, sign test).

The mean FUL (±SEM) after implantation of the device was 29.6 ± 8.5 mm. The mean FUL before implantation was 20.2 ± 8.1 mm and was statistically significant ($P < 0.001$, sign test). In the 11 male patients, urethral leakage pressure was measured by means of retrograde perfusion sphincterometry. Good correlation ($r = 0.88$) was seen between urethral leakage pressure and MUP with the cuff inflated. Correlation was 0.93 when the cuff was deflated. Thus the MUP and urethral leakage pressure did not differ significantly.

On cystometric investigations, normal bladder capacity and compliance were measured. Uroflowmetry showed normal maximal flow at voiding. Residual volumes were less than 30 ml.

Discussion

The success rate following implantation of an artificial urinary sphincter varies between 70 and 92% (Light and Scott, 1983; Diokno *et al.*, 1987; Goldwasser *et al.*, 1987). The most frequent causes of failure are erosion of the cuff through the urethral wall or infection. Disappointing results after re-operation are reported and often lead to definitive removal of the device (Light and Scott, 1983; Diokno *et al.*, 1987).

The condition and vascularisation of the urethral tissues are of crucial importance. When vascularisation is compromised as a result of previous urethral or anti-stress incontinence surgery, a higher erosion rate may be expected (Donovan *et al.*, 1985; Barrett, 1987b). The optimal position for placement of the cuff seems to be around the bladder neck (Diokno *et al.*, 1987), where vascularisation is better.

Factors that help to prevent erosion do so by reducing local high pressure and subsequent tissue compression; temporary low pressure is achieved by primary deactivation and nocturnal deactivation (Furlow, 1981; Goldwasser *et al.*, 1987).

The optimal cuff pressure to be determined during operation has not yet been established. Pressure should not be too high since the risk of insufficient vascularisation increases with pressure. A pressure regulating balloon in the 90 to 95 cm H_2O range is considered potentially dangerous (Lowe *et al.*, 1988). On the other hand, a low pressure system might fail to ensure continence. In most of our patients we installed the 60 to 70 cm H_2O pressure regulating balloon, which has been reported to result in a pressure generated by the cuff in the "continence zone" (Scott, 1978). A discrepancy between the pressure installed during operation and that measured during or after the procedure has been reported by Barrett (1987a), Goldwasser *et al.* (1987), Leach (1987) and Lowe *et al.* (1988). We found a pressure difference of 30.8%, which is equal to the pressure deficit measured in incontinent patients (Leach, 1987).

A lower urethral pressure is an advantage in cases of continence since tissue compression is less. The reason for achieving continence at these low pressures may possibly be attributed to the increase in FUL after cuff implantation.

Not only the pressure installed in the balloon but also a very careful measurement of cuff size is of crucial importance in assessing continence. The relation between small cuff size and the risk of erosion has been described previously (Furlow, 1981; Furlow and Barrett, 1985). We agree with Mundy and Stephenson (1984) that a low pressure device is less hazardous. When the optimal cuff size is determined by measuring it carefully and not by adjusting the size to the desired pressure, one need not fear that pressure will become too high.

The pressure deficit in our continent patients was higher than that reported by Lowe *et al.* (1988). We fail to understand how the 60 to 70 cm H_2O pressure regulating balloon, which the authors used in the majority of their patients, can exert a pressure around the urethra which is higher than 80 cm H_2O. This effect cannot be reached by extra filling of the balloon since overfilling by more than 20 ml will raise the pressure by less than 2%. If the high pressure is achieved by a snug fit of the cuff around the urethra, this is potentially dangerous, since persistent high pressure may compromise tissue vascularisation. Moreover, we expect the pressure of a snugly fitted cuff to remain high during the periods of deactivation, thus preventing the beneficial effects of deactivation. However, the pressure values with the cuff deflated are not reported by Lowe *et al.* (1988).

We do not know why the pressure is lower than that installed in the balloon during operation. Possible reasons are tissue atrophy under the cuff or fluid loss from the system. It was also noted that in 3 patients with different balloon pressures (51–60 cm H_2O in 1 and 71–80 cm H_2O in 2), intraurethral pressure values differed little from the pressure when a 61 to 70 cm pressure balloon was used (Table 2).

We compared our data from urethral pressure profilometry with data from retrograde perfusion sphincterometry and demonstrated a good correlation.

Since intra-urethral pressure may be lower than expected from the pressure in the pressure regulating balloon, careful pre-operative cystometry must be performed in order to detect detrusor abnormalities. The occurrence of instability after implantation of the sphincter device was described by Furlow and Barrett (1985), Roth *et al.* (1986) and Murray *et al.* (1988) and may lead to incontinence.

It was concluded that the maximal urethral pressure after implantation of the AMS 800 sphincter was significantly lower than would be expected from the values as installed in the pressure regulating balloon. Nevertheless, patients may be continent because of the significant increase in functional urethral length after placement of the cuff.

Acknowledgement

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Early Experience of the Gittes "No-incision" Pubovaginal Suspension for Stress Urinary Incontinence

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Summary—A series of 20 women with stress urinary incontinence underwent bladder neck suspension according to the method in which there are no suprapubic or vaginal incisions and no buttresses. Follow-up was between 9 weeks and 8 months. Twelve patients (60%) were cured, 2 (10%) were significantly improved and 6 (30%) were not improved; 3 patients had pre-operative detrusor instability; when they were excluded the failure rate fell to 23%. These results are inferior to those obtained in this unit using the Stamey procedure, although the difference is not significant. The operation is quick and easy to perform and was well tolerated with minimal complications; we believe it is worthy of further evaluation.

Needle bladder neck suspension was first described as a treatment for female stress incontinence by Pereyra (1959) and has subsequently undergone many modifications, notably by Stamey (1973), Pereyra himself (Pereyra and Lebherz, 1978) and Raz (1981). Of these the Stamey procedure has gained most popularity. Recently Gittes and Loughlin (1987) described a modification of the needle suspension that eliminates all incisions (henceforth referred to as the Gittes procedure). We report our early experience of this operation.

Patients and Methods

A series of 20 women with stress incontinence who would otherwise have had a Stamey needle suspension underwent the Gittes procedure. Their ages ranged from 36 to 76 years (mean 54); 9 had pure stress incontinence and 11 also had episodes of urgency or urge incontinence. All patients underwent pre-operative urodynamic assessment using Lectromed UIS 5000 apparatus; in 3 patients there was evidence of detrusor instability; the remainder were stable. Nine patients had had no previous pelvic surgery, 4 had undergone hysterectomy and 7 had had a total of 12 anti-incontinence procedures prior to referral. None of the patients had undergone previous needle suspensions.

The operation was performed as described by Gittes and Loughlin (1987). Under general anaesthesia and antibiotic cover with gentamicin and ampicillin, with the patient in the Lloyd-Davies position, the bladder was drained with a Foley catheter and the balloon left inflated. Using a Stamey needle, bilateral no. 1 monofilament nylon slings were passed from tiny suprapubic stab wounds 5 cm lateral to the midline to emerge through the vaginal wall below and lateral to the bladder neck. Using a no. 3 Mayo needle, the slings were incorporated in a mattress suture in the vaginal wall before being passed back up with the Stamey needle to emerge through the original suprapubic stab wounds. No vaginal incisions were made and no buttresses were used. Bladder neck mobility and bladder integrity were checked at the end of the procedure by cystoscopy before tying the slings. A 16F suprapubic catheter was inserted and the abdominal stab wounds were closed with a single suture. Early in the series a proflavin-soaked vaginal pack was inserted but this was later abandoned.

Post-operatively the suprapubic catheter was

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clamped after 48 h; latterly this was decreased to 24 h with no detrimental effect. Residual urine volumes were measured after each void and when these were significantly less than the voided volume the catheter was removed. The patient was allowed home soon after the suprapubic catheter was removed; in practice this was usually the next day.

Patients have been followed up and urodynamic assessment has been performed where indicated. The mean follow-up was 5 months (range 9 weeks–8 months). "Cure" was defined as total absence of post-operative incontinence (Stamey, 1980). "Significant improvement" was recorded in patients who experienced only rare minor leakages post-operatively.

Results

The results are shown in the Table. Twelve of the 20 patients were cured (60%) and 2 (10%) were significantly improved. The remaining 6 patients (30%) were not improved by the procedure. The mean age of these latter patients (52 years) was not significantly different from that of the whole group. Only 1 had had previous incontinence surgery. Two of the 6 had post-operative voiding problems (catheters *in situ* for 3 and 6 days after clamping); 5 of the 6 patients had pre-operative urge incontinence but only 2 had detrusor instability demonstrated by urodynamic assessment. If the patients with detrusor instability are excluded from the analysis, the overall cure rate becomes 11 of 17 patients (65%), with 2 patients (12%) significantly improved and 4 failures (23%).

The procedure was tolerated well and complications were few. In 1 patient, cystoscopy at the end of the procedure revealed that the bladder had been perforated and the slings had to be re-positioned. There were no problems associated with the stab wounds and in all but 1 patient, who complained of unilateral pelvic pain which may have been related to the sling, post-operative discomfort was transient and minimal. Nine patients (45%) developed a pyrexia of above 37.5°C post-operatively, although all patients received peri-operative antibiotics and in no case was there any evidence of pre-operative sepsis. Post-operative pyrexia was caused by urinary tract infection in 2 patients and by a chest infection in another, but was unexplained in the remaining 6 patients. All 6 patients with unexplained pyrexia had had vaginal packs *in situ* for the first 24 h, whereas packs were inserted in only 5 of the 11 women whose temperatures did not rise to 37.5°C ($P < 0.05$, Fisher's exact test).

Table Results of Gittes Bladder Neck Suspension in 20 Patients

	No	*(%)*
All patients		
Cured	12	(60)
Significantly improved	2	(10)
Failed	6	(30)
Detrusor instability excluded		
Cured	11	(65)
Significantly improved	2	(12)
Failed	4	(23)

The Figure shows the times which elapsed in each case before the suprapubic catheter was clamped, before the catheter was removed and before the patient was discharged. In the majority of cases post-operative voiding problems were absent or transient and catheters were removed a median of 2 days after they were clamped (range 1–11 days). Four patients (20%) had protracted difficulty voiding after their catheters were clamped and the catheters remained *in situ* for a further 6, 7, 9 and 11 days. Oral cholinergic agents were prescribed in 2 cases but no further surgical intervention was required and all patients were voiding satisfactorily at the time of discharge. The median post-operative stay was 5 days (range 3–13).

One patient reported that one of the slings might have snapped during a coughing fit 2 weeks after surgery and this was confirmed on vaginal examination. At a second operation the snapped sling was removed and a second sling inserted. Her subsequent recovery was uneventful.

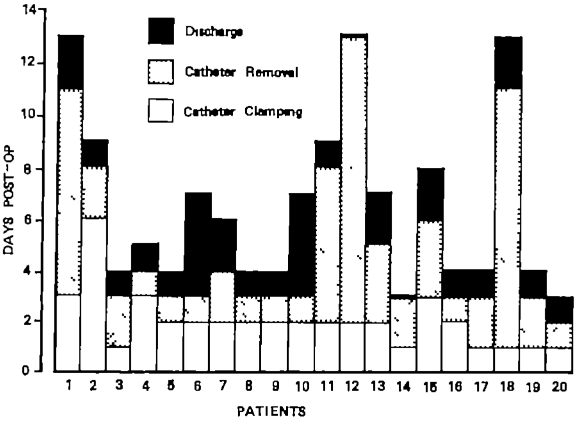

Fig. Time elapsed in each patient prior to clamping of suprapubic catheter, removal of catheter and discharge from hospital after the Gittes procedure.

Discussion

The results of this series are marginally though not significantly inferior to those of a series of 40 Stamey procedures performed in this unit on a similar group of patients (Wujanto and O'Reilly, 1989). In that series 31 patients (78%) were cured or significantly improved and there were 9 failures (22%), although when patients with unstable bladders were excluded the failure rate fell to 12%. In the present series of Gittes procedures only 3 patients had unstable bladders; 2 of these patients remained wet. There were no other factors in this series associated with an adverse outcome. As with other bladder neck suspension procedures, the critical feature is the tension of the sling, and with experience the results of the Gittes procedure can be expected to improve. In the series of Gittes and Loughlin (1987), in which there were 6 failures out of an overall total of 40 procedures, there were no failures among the last 14 patients. In the first half of the present series 6 women were cured or improved and there were 4 failures, and in the second half 8 women were cured or significantly improved, with only 2 failures.

The principal difference between the Gittes and the Stamey procedures is the absence in the former of suprapubic and vaginal incisions and of Dacron or Silastic buttresses. In the Gittes procedure the exposed nylon slings in the vaginal wall become covered by granulation tissue and then become epithelialised. The slings are therefore surrounded by scar tissue which acts as a natural buttress attached to both the sling and to the full thickness of the vaginal wall. Thus, unlike the Stamey operation, the Gittes procedure is not complicated by problems related to either the wounds, which we have previously encountered (Wujanto and O'-Reilly, 1989), or to the artificial buttresses, which have in some cases necessitated their removal (Mundy, 1983). Gittes and Loughlin describe how the mattress sutures cut through the vaginal wall and subcutaneous fat as they become epithelialised to allow return of the anterior vaginal wall to a normal resting position; this slow "cheese-wire" effect of the nylon on the underlying tissues, suggested by Mundy (1983) as a potent cause of post-operative pain in Stamey operations, does not appear to be a problem in Gittes procedures.

The Gittes procedure has certain advantages over the Stamey operation; it is quicker, taking around 10 to 15 min to perform, is less invasive and therefore less likely to lead to complications, and offers the potential for a shorter period of hospitalisation. In 14 patients in this series the suprapubic catheter was not clamped until the second post-operative day, as recommended by Gittes and Loughlin (1987). Our experience later in the series suggests that the catheter can be clamped after only 24 h without any adverse effects. Thus in many cases the catheter can be removed on the second day, with discharge from hospital on the third. In fact only 2 of the 6 patients whose catheters were clamped within 24 h went home on the third day; 3 were discharged on the fourth day and 1, who was unable to void initially, stayed until the thirteenth day. However, surgical trauma is minimal in this procedure and there is no reason why the fitter younger women should not be discharged on the same day with their catheters *in situ*, as advocated by Gittes and Loughlin. Indeed the operation could be performed under local anaesthesia in selected patients.

Discharge from hospital was delayed in 2 patients by unexplained pyrexia, which has not previously been reported as being a problem with needle suspensions. Such post-operative pyrexia in ou cases could have been related to the proflavin vaginal packs, which are advocated by Stame (1973) but not by Gittes and Loughlin. Omission o the packs was not associated with any advers sequelae and they are probably unnecessary.

In conclusion, the Gittes procedure is an alternative anti-incontinence operation which is simple to perform than other needle suspensions. Th incidence of complications is low. In this series 70% of patients with stress incontinence were cured o significantly improved. These results are comparable with the results of other needle suspension (Gaum *et al.*, 1984; Handley Ashken *et al.*, 1984 Wujanto and O'Reilly, 1989). While longer follo up is required, our early experience suggests tha this operation merits further evaluation.

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The Effects of Simple Hysterectomy on Vesicourethral Function

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Summary—Many women who present with symptoms of bladder dysfunction relate the onset to the operation of simple hysterectomy.

A group of 42 women undergoing simple hysterectomy was studied prospectively. Urinary symptoms, urodynamic findings and sacral reflex latencies (SRLs) were assessed pre-and post-operatively.

After hysterectomy the incidence of urinary symptoms increased from 58.3 to 75.0%. Vesicourethral dysfunction was altered in 30.6% of patients, 72.7% of whom had evidence of pelvic neuropathy as detected by SRLs.

The results show that simple hysterectomy is associated with a significant incidence of post-operative vesicourethral dysfunction and that there is an identifiable neurological abnormality incurred at operation which is pertinent to the subsequent disordered voiding.

Since the early studies of Hanley (1965, 1969) urologists and gynaecologists have become increasingly aware of the effects of simple (total) hysterectomy on the function of the urinary bladder and urethra.

To date no study has definitely linked hysterectomy with subsequent vesical and urethral dysfunction, but it is difficult not to incriminate the procedure because of the chronological relationship of the former to the latter. The aetiology and incidence of lower urinary tract dysfunction after this operation are unclear and may be influenced by several factors.

Previous studies undertaken to investigate urinary problems in women undergoing hysterectomy have been limited either solely to subjective analysis (Kilkku *et al.*, 1981; Kilkku, 1985; Jequier, 1976) or to post-operative subjective analysis (Wake, 1980).

With the recent introduction of neurophysiological tests to complement urodynamic studies of vesicourethral and pelvic floor function, it is now possible to define more accurately the effect of simple hysterectomy upon micturition and the aetiology of any resulting dysfunction.

This study was undertaken to determine the incidence of pre- and post-operative urinary symptoms in women undergoing simple hysterectomy, to relate the findings of the pre- and post-urodynamic assessments, and to investigate whether this operation may be responsible for a pelvic neuropathy pertinent to subsequent post-operative vesicourethral dysfunction.

Patients and Methods

Forty-two women, mean age 43.3 years (range 28–68) and mean parity 2.6 (range 0–5), who presented to the Department of Gynaecology were enrolled in the study. All had presented primarily with gynaecological symptoms and were awaiting simple hysterectomy for benign disease of the uterus and adnexae.

None had undergone previous bladder or urethral

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surgery or pre-operative urological investigation apart from culture of a mid-stream specimen of urine.

No patient had any overt neurological or psychiatric disorder, history of malignant disease or diabetes mellitus.

Pre-operative evaluation. The patients were interviewed prior to surgery to identify any urinary symptoms. Those specifically determined were diurnal frequency of micturition (judged to be present if voiding more than 6 times a day), nocturia (waking to void more than once a night), urgency, urge/stress incontinence, uralgia, hesitancy, reduction of the stream, sensation of incomplete bladder emptying and haematuria.

Each patient underwent medium fill videourodynamics performed in the supine position, with provocative cystometry and voiding studies in the seated position.

All women had SRL measurement at the time of urological evaluation as previously described (Galloway *et al.*, 1985; Parys *et al.*, 1987).

The sensory threshold of the dorsal nerve of the clitoris (DN) and of the urethral sphincter mucosa (US) was noted as the voltage at which the patient first perceived the stimulus. The conduction latencies from the DN to the urethral (US) and anal (AS) sphincters, and from the US to AS were measured and the results compared with controls.

Fifteen sex and age matched women (mean age 42.8 years, range 31–67) who were urologically and neurologically normal were used as controls for the SRL study. The sensory thresholds and conduction latencies of the controls are detailed in Table 1. Abnormal conduction times for the DN to US and DN to AS were defined as greater than 45 ms, *i.e.* more than 2 standard deviations from the mean, and a US to AS latency in excess of 80 ms was considered abnormal.

In order to establish the reproducibility of the SRL technique, the nerve conduction studies were repeated in 9 women 6 weeks after initial assessment.

Post-operative evaluation. Patients were reassessed symptomatically and the urodynamic and SRL studies were repeated at an interval of 3 to 6 months (mean 4.7) after hysterectomy to exclude any short-term effects of pelvic surgery and yet minimise the hormonal sequelae of total or partial oophorectomy. The type of hysterectomy performed was determined by the underlying gynaecological pathology

Table 1 Sacral Reflex Latencies—Control Values

Sensory threshold/volts	*Controls (n=15) (range)*	
Dorsal nerve	28.3*	(20–40)
Urethral sphincter	29.0†	(15–50)
Latency/ms		
DN - - US	37.3**	(31–42)
DN - - AS	35.8††	(29–42)
US - - AS	59.9‡	(47–71)

DN = Dorsal nerve of clitoris.
US = Urethral sphincter
AS = Anal sphincter.
* S.D. = ±5.2
† S.D. = ±9.5
** S.D. = ±2.9
†† S.D. = ±3.6
‡ S.D. = ±7.6

Thirty-six women (mean age 42.9 years, range 28–67) were available for follow-up after undergoing simple hysterectomy.

Of the 42 women originally entered in the study, 6 were excluded from the final analysis for the following reasons:

1. Three were lost to post-operative follow-up.
2. On admission 2 were deemed not to require hysterectomy.
3. One emigrated prior to admission for surgery.

Total abdominal hysterectomy was carried out in 91.7% (33/36) of women, of whom 55.6% (20/36) had both ovaries preserved and 19.4% (7/36) had one ovary conserved. Total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed in 16.7% (6/36); 3 women (8.3%) had a vaginal hysterectomy.

Methods, definitions and results conform to the standards recommended by the International Continence Society, except where specifically stated.

Results

Symptomatic review. The number of women who complained of urinary symptoms increased significantly from 21/36 (58.3%) pre-operatively to 27/36 (75.0%) post-operatively (McNemar's test $\chi^2 = 6.0$; $0.02 > P > 0.01$).

No woman became asymptomatic after hysterectomy but 2 had a distinct improvement in their symptoms. In both cases stress incontinence was improved as a result of the development of urethral obstruction.

The pre- and post-operative incidence of each urinary symptom is listed in Table 2. No single

Table 2 Incidence of Urinary Symptoms in 36 Patients before and after Hysterectomy

Before hysterectomy		*After hysterectomy*
17	Frequency	26
15	Urgency	20
15	Incontinence	18
10	Incomplete emptying	19
7	Nocturia	11
4	Uralgia	4
2	Hesitancy	3
2	Poor stream	4
2	Strain void	4
0	Haematuria	0

symptom was significantly more common post-operatively (McNemar's test).

Urodynamics. Pre-operative videocystourethrography confirmed lower urinary tract dysfunction in 14/36 patients (38.9%) (Table 3). After hysterectomy a new urodynamic abnormality was found in 11/36 women (30.6%). The 95% confidence interval for the proportion developing dysfunction was (15.0, 46.0). Genuine urinary stress incontinence was the most common finding (Table 3).

In those cases where vesicourethral function was altered after hysterectomy, 5 developed genuine urinary stress incontinence, 3 urethral obstruction, 2 detrusor instability and 1 genuine urinary stress incontinence with urethral obstruction. No asymptomatic woman had an abnormal urodynamic evaluation.

Seven of the 11 women with dysfunctional voiding after operation had no pre-operative abnormality. Only 4 women had a urodynamic abnormality pre-operatively. Two with genuine stress incontinence before hysterectomy developed urethral obstruction, and of 2 patients with pre-operative detrusor instability, 1 developed concomitant urethral obstruction and the other mixed urge/stress incontinence.

Altogether 21/36 women (58.3%) had abnormal post-operative urodynamics. No relationship could be inferred between the type of hysterectomy and any specific vesicourethral dysfunction.

Sacral Reflex Latencies. The reproducibility of SRL measurements was confirmed; no significant variation was found in any parameter on retesting ($0.05 > P > 0.1$; paired *t* test) (Table 4).

Sensory Thresholds. All pre-operative sensory thresholds were normal when compared with the controls. Although the DN and US sensory thresholds were elevated after operation, the rise was not significant (Table 5). Seven women (19.4%), however, had significant elevation of one (2 DN; 2 US) or both sensory thresholds (greater than 2 standard deviations from the mean), of whom 4 had altered vesicourethral function after operation.

Reflex Latencies. Pre-operative conduction latencies were normal in 35/36 women. The one patient with abnormal responses, who was found to have genuine stress incontinence, had prolonged DN to US, DN to AS and US to AS latencies (51, 56, 105 ms respectively) (Figs 1, 2, 3). These remained abnormal after hysterectomy. There was no significant difference between the reflex responses of the pre-operative group and the controls.

After hysterectomy, analysis of all 36 women showed a significant prolongation of all 3 reflex arc latencies compared with pre-operative values (Table 5).

After operation, a further 10 patients had prolonged DN to US and DN to AS reflex latencies (>45 ms) (Figs 1, 2, 3). In 3, although symptoms were more marked after operation, the urodynamic abnormalities were unchanged. Ten of the 11 women who had prolongation of the above latencies

Table 3 Incidence of Urodynamic Abnormalities

	Detrusor instability (%)	*Urethral obstruction (%)*	*Stress incontinence (%)*	*Normal (%)*
Before hysterectomy	6* (16.7)	1 (2 8)	9* (25.0)	22 (61.1)
After hysterectomy	8† (22.2)	5† (13.9)	13† (36.1)	15 (41.7)

* = 2 patients with detrusor instability + stress incontinence.
† = 5 patients with dual vesicourethral dysfunction
(3 detrusor instability + stress incontinence)
(1 detrusor instability + urethral obstruction)
(1 urethral obstruction + stress incontinence).

Table 4 Reproducibility of Sacral Reflex Latencies—Mean Sensory Thresholds

Sensory threshold/volts	*First assessment (n=9) (range)*	*Second assessment (n=9) (range)*
Dorsal nerve	29.4 (25–40)	29.2 (25–40)
Urethral sphincter	25.0 (20–30)	25.2 (20–30)
Latency/ms		
DN – – US	36.6 (25–41)	36 8 (26.42)
DN – – AS	36.2 (25–46)	36.0 (25–44)
US – – AS	63.4 (55–72)	63.1 (56–70)

DN = Dorsal nerve of clitoris.
AS = Anal sphincter
US = Urethral sphincter mucosa.

also had abnormal US to AS responses. All women who had elevated sensory thresholds had prolonged SRLs.

Altogether 11/36 hysterectomised women (30.6%) had evidence of a mixed motor/sensory pelvic nerve neuropathy, of whom 8/11 (72.7%) had altered vesicourethral function after operation.

No neurological abnormality was detected in any woman with normal lower urinary tract function.

Discussion

During the operation of simple hysterectomy the pelvic plexus may be at risk in 3 areas:

(1) Division of the lateral ligaments of Mackenrodt places at risk the main branches of the plexus passing beneath the uterine arteries (Smith and Ballantyne, 1968).

(2) The major part of the vesical innervation enters via the bladder base, then spreads throughout the detrusor muscle, and may be damaged during blunt dissection of the bladder, the uterus and cervix.

(3) Extensive dissection of the paravaginal tissues may disrupt the pelvic neurones passing around the lateral aspect of the vagina.

Therefore, during simple hysterectomy accurate and careful dissection should be a matter of course to minimise symptoms resulting from nerve damage to the bladder and urethra. The dissection should be kept as close as possible to the uterus with minimal mobilisation and excision of the vagina, and careful separation of the bladder base from the uterus and cervix.

This study confirms that urinary symptoms are common in women awaiting hysterectomy. The incidence in this study (58.3%) is comparable to the figure of 62% reported by Jequier (1976). The marked disparity of almost 20% between the incidence of urological symptoms and the rate of urodynamic abnormality is difficult to explain. If some urinary symptoms were related to the gynaecological pathology, the difference should not have been maintained after hysterectomy. It may be that the urinary dysfunction in some patients was of such a subtle nature that videocystometry was not sensitive enough to detect it.

In this study 30.6% of women had altered vesicourethral dysfunction after simple hysterectomy, of whom 72.7% had evidence of pelvic neuropathy, demonstrating that this operation has a significant and deleterious effect on the lower urinary tract. Thus it is important to consider the aetiology and possible prevention of these abnormalities.

Genuine urinary stress incontinence. This may occur either as a result of direct intra-operative damage

Table 5 Sacral Reflex Latencies before and after Hysterectomy

Sensory threshold/volts	*Before hysterectomy (n=36) (range)*	*After hysterectomy (n=36) (range)*	*Paired t test*
Dorsal nerve	28.1 (20–40)	30 1 (20–55)	$0.5 > P > 0.1$
Urethral sphincter	29.6 (12–50)	33.0 (10–75)	$0 5 > P > 0.1$
Latency/ms			
DN – – US	36 8 (19–51)	41.2 (22–74)	$0.02 > P > 0.01$
DN – – AS	35.8 (23–56)	40.8 (25–84)	$0.02 > P > 0.01$
US – – AS	61 3 (44–105)	70.3 (47–108)	$0.01 > P > 0.001$

DN = Dorsal nerve of clitoris
US = Urethral sphincter.
AS = Anal sphincter.

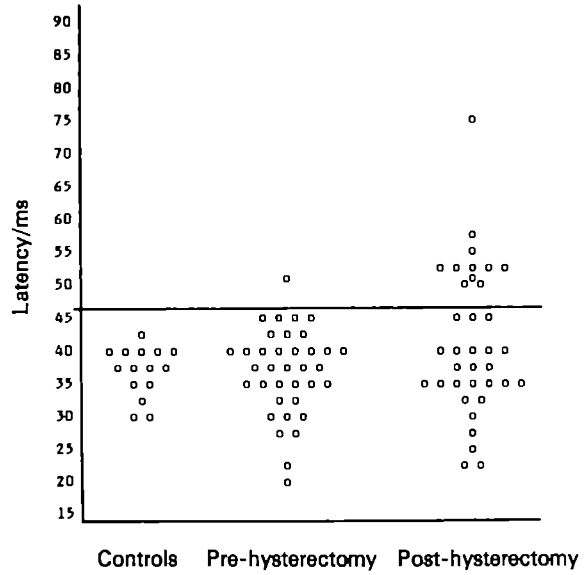

Fig. 1 Distribution of dorsal nerve to urethral sphincter latencies.

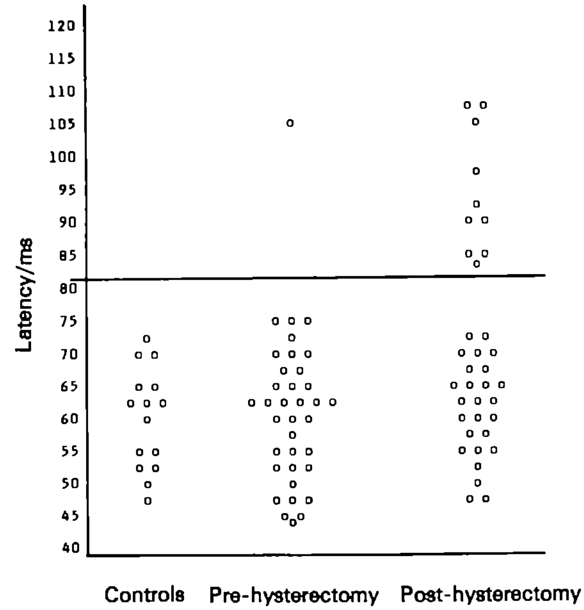

Fig. 2 Distribution of dorsal nerve to anal sphincter latencies.

to the pelvic muscles, or because of muscle weakness secondary to pelvic nerve damage (Snooks *et al.*, 1985). Two-thirds of the women who developed this abnormality had prolonged SRLs, indicating that pelvic neuropathy might be implicated in this disorder.

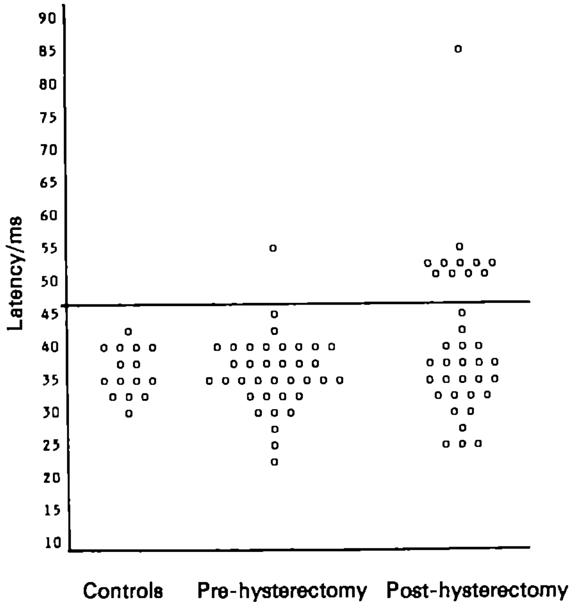

Fig. 3 Distribution of urethral sphincter to anal sphincter latencies

Urethral obstruction. All 4 women who developed urethral obstruction after hysterectomy had abnormal pelvic nerve conduction studies which were previously normal. In 2 patients, mid-urethral obstruction may have resulted in smooth muscle supersensitivity to circulating catecholamines secondary to post-ganglionic nerve section following urethral dissection (Parsons and Turton, 1980), with consequent sphincter spasticity and outflow obstruction.

The other 2 women were obstructed at the bladder neck; this was probably caused by bladder neck and periurethral fibrosis (Smith *et al.*, 1970), with concomitant nerve damage.

Detrusor instability. Pelvic neuropathy was also detected in one of the women who developed detrusor instability after hysterectomy. Intra-operative partial pre-ganglionic denervation of the pelvic plexus may cause a detrusor muscle sensitivity or increased activity in the intramural ganglia, which results in instability.

The purpose of this study has not been to detract from or question the value of simple hysterectomy, which is a widely accepted and highly effective procedure, but to highlight the fact that this operation can have important and sometimes distressing sequelae which can occur as a result of damage to the vesicourethral innervation. Women with gynaecological symptoms should be carefully selected, with consideration being given to alternative therapy options, and if surgery is necessary, meticulous attention should be paid by the surgeon to operative technique.

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Burch Colposuspension or Sling for Stress Incontinence? A Prospective Study using Transrectal Ultrasound

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Summary—Twenty-nine women with stress incontinence were treated surgically by Burch colposuspension or ox fascial sling. The operation was selected prospectively according to the transrectal ultrasound appearance of the bladder neck and urethra during stress. Two groups were defined according to the extent of bladder neck descent and posterior rotation during stress: Type I (minimal descent, *i.e.* < 1.5 cm) and Type II (downward posterior rotational movement). Success rates of 76% are reported and the action of each procedure discussed.

The criteria for the selection of one operation for the treatment of stress incontinence as opposed to another is anecdotal and based on an individual surgeon's preference. Success rates are variable but there is evidence to suggest that the best results are achieved using the suprapubic route (Stanton and Cardozo, 1979; Ostergard, 1985). At present, most surgeons use the Burch colposuspension as the primary incontinence operation, reserving the sling procedure for recurrent incontinence when other operations have failed. However, the pathological mechanisms of incontinence do not seem to have been taken into account in the selection of which operation is most suitable for each patient.

We conducted a prospective study to select a suprapubic surgical procedure from the anatomical relationships of bladder, urethra and symphysis pubis viewed by transrectal ultrasound (Richmond *et al.*, 1986).

Patients and Methods

Twenty-nine consecutive female patients with urodynamically confirmed genuine stress incontinence (GSI) were studied. All methods, definitions and abbreviations conform to those described by the International Continence Society (Bates *et al.*, 1979). Investigation included a perineal pad weighing test, urine flowmetry, medium-fill water cystometry, urethral pressure profile measurement (UPP) and fluid bridge testing (FBT). If surgery was recommended the patient was scanned using an Aloka SSD-210 DX with linear array transrectal probe. The bladder was filled to a standard volume of 250 ml. The urethrovesical junction was marked using computer software. Each patient was scanned supine and in the erect position at rest and during stress.

Seven measurements were made from polaroid films taken from video pictures using a single frame freeze facility (Richmond and Sutherst, 1989). Each patient acted as her own control. The symphysis pubis was used as the reference point. (Although the angle of inclination and width of the symphysis vary from patient to patient, they remain constant for each individual and can therefore be used as a template for comparison of the resting and straining images).

The following measurements were made. The midline of the symphysis was obtained by drawing a line between 3 points equidistant from the anterior and posterior surfaces; this was extended to bisect

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the urethra. A further line was drawn along the proximal 1 cm of the urethra and extended to meet the symphysis axis line. By drawing a vertical tangent at the junction of the axis line and the bony shadow of the symphysis, the angle A or bearing of the bladder neck in degrees of a clockwise arc could be measured. Angle B was the urethral angle of the proximal 1 cm of urethra in degrees clockwise from the vertical. Angle C was the posterior urethrovesical angle and angle D corresponded to the angle in a clockwise arc subtended by the axis line and its vertical at the junction with the symphysis.

Three distances were then measured (in cm). X was the distance from the symphysis to the internal urethral meatus. Y was the distance from the symphysis to the urethra along the axis line and Z was the line from the internal urethral meatus to the junction with the extended symphysis axis line (Fig. 1).

Seven measurements from each resting and straining position were therefore available for comparison. These recorded the maximum change in the position of the urethrovesical junction, angle or urethral inclination and bearing of the urethrovesical junction from the vertical.

If the bladder neck moved less than 1.5 cm either vertically or associated with posterior rotation during stress, a Burch colposuspension was performed. When descent greater than this occurred in conjunction with posterior rotation, a sling was performed (Fig. 2). All 29 patients were reviewed 6 months after surgery and the investigations repeated.

Results

Using the selection criteria described, 15 patients had a Burch colposuspension and 14 an ox fascial sling operation. The mean age and parity were similar for both groups. The procedure was a primary incontinence operation for 12/15 colposuspension patients and 9/14 sling patients. Overall, 22 patients (76%) were cured (stable bladder with pad test < 1.0 ml/h).

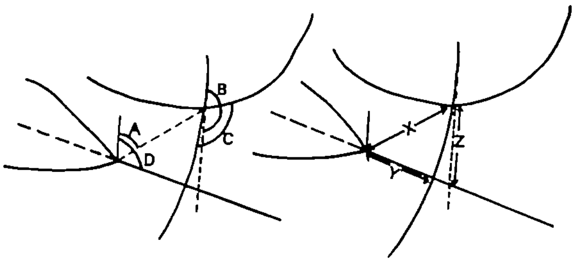

Fig. 1 Schematic drawing of ultrasound measurements (A, B, C and D are angles measured in a clockwise arc, X, Y and Z are measurements in cm).

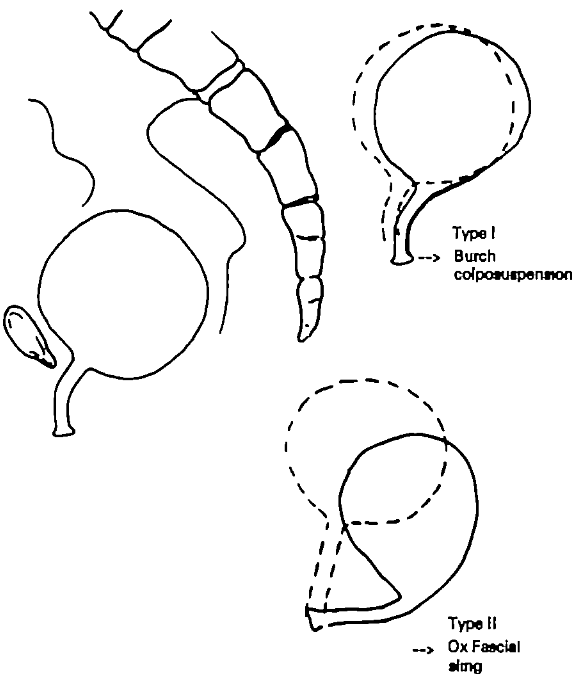

Fig. 2 Schematic drawing of surgical procedures performed for Type I and Type II groups.

Burch colposuspension

The success rate in patients undergoing a Burch colposuspension procedure was 87%. Two patients in this group were incontinent post-operatively. One of these developed detrusor instability and the other was a technical failure, *i.e.* there was no difference in the position of the bladder neck after surgery.

Sling operation

Five patients from the sling group were incontinent after surgery but had stable bladders. In 3 cases the sling made no difference to the anatomical relationships on scan and these operations should be regarded as technical failures. In this subgroup of incontinent patients there were no significant differences between the resting and straining ultrasound relationships pre-operatively from those measured post-operatively. The sling had not achieved anything and mobility of the bladder neck was still present. In the other 2 cases the patients were symptomatically better and although they demonstrated a cough-competent bladder neck mechanism during urethral stress testing, they leaked urine when exercising; 87% of the slings were successful when the surgical aim was achieved (provision of support for the posterior aspect of the bladder neck to prevent descent and rotation outwith the abdominal pressure transmission area during stress).

Significant difference ($P<0.05$) between the pre- and post-operative transrectal scan appearance were seen only in the successful Burch and sling operations (Tables 1 and 2). No differences were observed in the failed procedures. In these cases the operations had failed to elevate or support respectively.

Comparison of pre- and post-operative urodynamic results for the Type I and Type II procedures showed a significant reduction in the mean flow rate (MFR $P=0.007$) and also maximum closure pressure (MCP $P=0.001$). The peak flow rate (PFR), functional length of the urethra (FL) and bladder capacity (F3) were not significantly changed from the pre-operative values (Table 3).

Table 1 Difference between Straining and Resting Values before and after Surgery for Continent Burch Colposuspension Patients

Variable	*Mean difference*	*T value*	*P*
X	−0.11	−0.87	0.397
Y	0.24	1.20	0.253
Z	−0.79	−3.01	0.010*
A	24.00	3.94	0.002†
B	14.86	3.55	0.004†
C	9.14	1.16	0.266
D	0.35	0.15	0.884

* $0.01<P<0.05$
† $0.001<P<0.01$

Table 2 Difference between Straining and Resting Values before and after Surgery for Continent Sling Patients

Variable	*Mean difference*	*T value*	*P*
X	0.30	3.60	0.007†
Y	0.30	3.09	0.015*
Z	−0.91	−2.70	0.027*
A	33.22	3.43	0.009†
B	33.67	4.03	0.004†
C	47.1	4.70	0.002†
D	2.56	0.67	0.520

* $0.01<P<0.05$
† $0.001<P<0.01$

Table 3 Pre- and Post-operative Comparison of Urodynamic Results (mean and standard deviation)

	Before surgery		*After surgery*	
	Mean	*SD*	*Mean*	*SD*
PRF (ml/s)	24.2	33.6	31.0	12.4
MFR (ml/s)	16.6	6.9	12.4	4.7*
F3 (ml)	560.2	179.7	550.4	127.8
MCP (cmH_2O)	2.7	0.6	2.5	0.6†
FBT (cm supine)	1.6	0.5	0.6	0.6
FBT (cm erect)	1.7	0.4	0.2	0.4

* (MFR $P=0.007$)
† (MCP $P=0.001$)

Discussion

Following evaluation of a transrectal ultrasound technique to screen the bladder and urethra (Richmond, 1986), 2 main groups of incontinent women were defined on the basis of the anatomical changes occurring with stress. In 1 group (Type I), the bladder neck region appeared relatively immobile with minimal descent during stress (<1.5 cm). These patients still had an incompetent urethrovesical junction and urine loss occurred with stress. Presumably this was because of periurethral fibrosis limiting the normal urethral closure mechanism or because of a failure of the striated musculature of the pelvic floor to maintain urethral closure during increased abdominal pressure. The other group (Type II) demonstrated considerably greater bladder neck mobility. These patients were incontinent because of inadequate pressure transmission to the proximal urethra during stress.

We adopted the principle that when descent and rotation of the bladder neck occurred as a result of stress, as seen on ultrasound, support by a sling was required to maintain the position of the urethrovesical junction during increased intra-abdominal pressure. If the urethrovesical junction was relatively "fixed", *i.e.* already in an intra-abdominal position, some other mechanism was needed to close it during stress. This could be by Burch colposuspension, which we believe works by compression of the proximal urethra against the posterior surface of the symphysis during stress. The adoption of this policy has proved satisfactory and appears to provide a more rational approach to surgical selection.

The unanswered question is how to predict the sling failures. In this study, 3 patients who had a sling operation were symptomatically much better after surgery. They had cough-competent bladder neck mechanisms on urethral stress testing but still leaked urine during exercise. There was no evidence of a fistula. These failures are difficult to explain. It is possible that during daily exercise activities the sling, which is anchored to the rectus sheath, fails to provide any support and only becomes effective when the recti are under tension, *e.g.* coughing. In some circumstances where there is excessive bladder neck mobility during stress, simply providing a platform for the bladder base and proximal urethra may be inadequate; elevation is also required, so that with the support of a sling, pressure transmission will be adequate to keep the proximal urethra closed. It is possible that intra-operative screening by ultrasound coupled with urethral stress testing may help to improve the cure rate in this group with difficult clinical problems.

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Phase II Study of Carboplatin in Locally Advanced and Metastatic Transitional Cell Carcinoma of the Urinary Bladder

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Summary—Twenty-five previously untreated patients with measurable locally advanced and/or metastatic transitional cell carcinoma of the urinary bladder were included in a phase II study with carboplatin. Bolus injections were administered in 2 courses every 4 weeks at an initial dose of 400 to 450 mg/m^2 with the option of increasing the dose to 450 to 500 mg/m^2 in individual patients during the second cycle, depending on haematological toxicity. Two patients had a complete response (CR), 13 showed no change (NC) and 9 had progression of disease (PD), including 4 early progressions. There was no delay in treatment because of myelosuppression. Thrombocytopenia led to a reduction in drug dosage. No reduction in renal function was observed. Increased dosage did not increase the response rate.

This study indicated the low effectiveness of single agent carboplatin in transitional cell carcinoma of the urinary bladder.

The most effective drugs in the treatment of transitional cell carcinoma of the urinary tract are cisplatin and methotrexate, which are reported to yield response rates of 50 to 70% if given in combination (Oliver *et al.*, 1986; Denis *et al.*, 1987; Stoter *et al.*, 1987; Yagoda, 1987). However, the side effects may be considerable and treatment is not possible in patients with reduced renal function or severe cardiac disease, both frequently found in elderly patients with bladder cancer. In order to identify other compounds effective in bladder cancer we carried out a phase II trial with the less nephrotoxic cisplatin analogue carboplatin in patients with locally advanced or metastatic transitional cell carcinoma of the urinary bladder.

Patients and Methods

A series of 25 previously untreated patients (21 males, 4 females) with bidimensionally measurable locally advanced or metastatic transitional cell carcinoma of the urinary bladder gave their informed consent to enter the study. The median age was 62 years (range 30–75). Histological grades II and III (W.H.O) were seen in 3 and 22 patients respectively. Eligibility criteria were: age $= < 75$ years, life expectancy at least 3 months and performance status $= < 2$ (W.H.O.), leucocyte count $= > 3 \times 10^9$/l, platelets $= > 100 \times 10^9$/l, serum creatinine < 125 µmol/l and creatinine clearance > 60 ml/min. The latter 2 criteria were subsequently changed to < 150 µmol/l and > 55 ml/min. Carboplatin was dissolved in a 500 ml 0.9% saline solution and administered intravenously in 2 courses at an initial dose of 400 mg/m^2 as a 30-min infusion every 4 weeks without pre- or post-hydration (dose level I, Table 1). Metoclopramide 40 mg and dexamethasone 20 mg were given as a standard prophylactic anti-emetic regime before every cycle. Haematological toxicity was evaluated weekly during 46 treatment cycles. Since no significant nephrotoxicity or myelotoxicity (necessitating reduction in

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Table 1 Chemotherapy

Dose level	*Cycle I (mg/m²)*	*No of patients*	*Cycle II (mg/m²)*	*No of patients receiving intended dose*
I	400	8	400	8
II	400	8	450	5
III	450	9	500	1

treatment) was observed in the first 8 patients, the dose in the second cycle in the subsequent 8 patients was increased to 450 mg/m^2 (dose level II) if sufficient nadir counts were found (leucocytes $> 3 \times 10^9$/l, platelets $> 100 \times 10^9$/l). Significant myelotoxicity did not occur during the first cycle and a further 9 patients started at 450 mg/m^2 with the option of increasing the dose in the second cycle to 500 mg/m^2 (dose level III) in cases of sufficient haematological nadir values. Nadir values of W.H.O. grade III and IV led to dose reductions of 25% during the second course.

All patients in whom the primary tumour represented the indicator lesion had a CT scan of the bladder with measurement of the largest tumour area (Sager *et al.*, 1987). After 2 courses of carboplatin the patients were evaluated by a further CT scan. Response was assessed as recommended by the W.H.O. (1979) handbook. Cystoscopy and rectal exploration under general anaesthesia were performed before entry to the study and at the time of evaluation. If the response assessed by CT differed from the clinical assessment, the CT evaluation was used. In addition to the W.H.O. criteria, the NC group comprised a subgroup of minor responses which were defined as a tumour reduction between 25 and 50%. Early progression was defined as significant tumour increase or death due to the malignancy at any time after the start of the first cycle and before the evaluation. The duration of response could not be assessed as all responding patients received immediate alternative treatment after therapy with carboplatin.

Results

Evaluation of tumour response

All but 1 patient were evaluated for response. One patient at dose level I died of cardiac disease (unrelated to treatment) before evaluation could be performed. We observed 2 CR (8%; 95% confidence limits, 0–19%), 13 NC and 9 PD including 4 early progressions (Table 2); 3 patients in the NC group showed minor responses. The responses were observed at dose levels I and III respectively. As shown in Table 3, complete responses were obtained in the 2 patients with the smallest tumours. The 3 patients with minor responses also had small tumours initially. Four patients had an evaluable bladder tumour and lung metastasis. In 2 of them the lesions at the 2 sites remained stable. In 1 patient there was progression at both sites. The bladder tumour in the fourth patient showed a minor response, but new metastatic lesions developed in the lung during treatment, signifying progression.

Table 2 Response to Carboplatin

Indicator lesions	*No.*	*CR*	*PR*	*NC (minor response)*	*PD (early progression)*
Bladder	19	2		13 (3)	4 (2)
Lung	6*			2	4
Lymph node	1			1	
Liver	2				2 (2)
Total	28	2	0	16	10

*Four patients had evaluable lung metastasis in addition to bladder tumour.

Toxicity

Thrombocytopenia, most pronounced at dose level III (Table 4), led to a reduction in drug dosage. Nadir counts occurred between days 15 and 22 with recovery to normal values during the fourth week.

Table 3 Responses in Relation to Initial Bladder Tumour Area

Response	*No*	*Mean tumour area (cm²)*	*Range*	*Mean tumour reduction (%)*	*Range*
CR	2	1.85	1.8–1.9	100↓	—
Minor response	3	2.7	2–4	39↓	30↓ 47↓
NC	8	27	7.6–86	1.5↓	21↓ 15.5↑
PD	2	5.6	2.2–9	73↑	33↑ 133↑
Early progression	2	16.9	16–17	—	—

↓ Regression ↑ Progression

Table 4 Haematological Toxicity

Dose level	*I*		*II*		*III*	
Cycle	*1*	*2*	*1*	*2*	*1*	*2*
WBC count ($\times 10^9$/l)						
Median nadir value	4.1	4.3	7.3	5.5	2.9	4.5
Minimum	3.2	3.2	3.7	2.1	2.4	2.6
Maximum	6.8	9.1	7.8	6.6	7.5	5.6
Platelet count ($\times 10^9$/l)						
Median nadir value	112	133	162	156	48	102
Minimum	61	110	90	94	7	16
Maximum	156	198	257	254	229	211

One patient with bilateral hydronephrosis and early progression had the most pronounced thrombocytopenia (7×10^9/l on day 15). There was no delay in treatment because of myelosuppression.

The individual platelet nadir values were significantly related to the patient's maximum serum creatinine values observed during the treatment period, even though the serum creatinine values remained within the normal range. At dose level III, an increased dose was administered to only 1 patient. One patient received 2 equal doses because of ileus between the cycles. Five patients received a reduced second dose because of thrombocytopenia (W.H.O. grades III and IV in 3 and 2 patients respectively). The last 2 patients at dose level III showed early progression after the first cycle and did not receive further chemotherapy. No grade III/IV leucocytopenia or treatment-induced anaemia was seen.

Nausea and vomiting were generally tolerable and limited to the day of treatment. However, 5 patients showed more severe and prolonged gastrointestinal toxicity (4 patients grade III, 1 grade IV).

Renal function was not affected by carboplatin chemotherapy, even in 4 patients with initial creatinine values between 125 and 150 µmol/l. One patient with early tumour progression developed post-renal uraemia due to increasing ureteric obstruction.

No ototoxicity, neurotoxicity, electrolyte or liver enzyme disturbances were found.

Discussion

Our response rate of 8% confirms other observations of the low activity of single agent carboplatin given as bolus injections every fourth week in transitional cell carcinoma of the bladder (Creekmore *et al.*, 1986; Germa *et al.*, 1987; Medical Research Council, 1987; Ogawa *et al.*, 1987). However, its activity may be greater than observed in this study since among our 3 minor responses, 1 patient was very close to a partial response (47% tumour reduction). Increased dosage did not seem to increase the response rate. Carboplatin 400 mg/m^2 represents an adequate initial dose in patients with advanced urothelial cancer, with the option of increasing the dose to 450 to 500 mg/m^2 in individual patients during the second cycle. Doses above this level are probably not feasible. Thrombocytopenia was the main objective side effect (Table 4). As shown by Calvert *et al.* (1985), the grade of thrombocytopenia is related to renal function. This may be more pronounced in elderly bladder cancer patients with reduced renal function reserve due to age (Dodion, 1987). As observed in other studies, nephrotoxicity was not a major clinical problem, even in the 4 patients with slight pre-treatment impairment of renal function (Germa *et al.*, 1987; Goren *et al.*, 1987; Medical Research Council, 1987; Tait, 1988; van Glabbeke *et al.*, 1988). However, we observed an increased creatinine value during carboplatin treatment in 1 of our patients with early progression. This was due to increasing ureteric obstruction and progression of the primary tumour rather than to drug toxicity.

A response rate of 8% incidates the low effectiveness of bolus injections of single agent carboplatin in transitional cell carcinoma of the urinary bladder. The major side effect was dose-related thrombocytopenia. The overall toxicity of the drug was acceptable using an initial dose of 400 mg/m^2 and increased dosage following nadir blood cell counts. Nephrotoxicity was not a clinical problem. We do not believe that carboplatin will play a major part as a single drug in the treatment of transitional cell carcinomas of the urinary tract, although its role in combination chemotherapy has yet to be explored.

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The Fate of G3pT1 Bladder Cancer

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Summary—Poorly differentiated (G3) cancers are known to have a worse prognosis than other superficial bladder tumours. In the period 1976 to 1987, 53 patients with G3pT1 disease were treated by radical radiotherapy with a 5-year survival rate of 64%. Thirteen patients (25%) developed an invasive tumour during the follow-up period. The presence of secondary carcinoma *in situ* was associated with a poor prognosis. These results are better than those reported for transurethral resection alone and suggest that radiotherapy is the treatment of choice in G3 superficial tumours.

The treatment of superficial (pTa and pT1) (UICC, 1978) bladder cancer remains controversial. The majority of tumours are well differentiated (G1) and may be safely managed by transurethral resection, but the small minority of undifferentiated (G3) tumours have a worse prognosis, with a 5-year survival rate of less than 20% (Pocock *et al.*, 1982; Heney *et al.*, 1983) and a progression to invasion in approximately 50% (Jakse *et al.*, 1987; Abel *et al.*, 1988) if managed by endoscopic means alone.

A previous study of T1 tumours from this centre (England *et al.*, 1981) found that patients with poorly differentiated carcinomas had a high incidence of disease progression and death. It has been our practice to offer patients with G3pT1 tumours a course of radical radiotherapy—as though the cancer were invasive (Blandy *et al.*, 1980; Jenkins *et al.*, 1988).

Patients and Methods

All patients with bladder cancer seen at the London Hospital between 1976 and 1987 were identified through the records of the Department of Pathology. The case notes of 53 patients with a histological diagnosis of G3pT1 transitional cell carcinoma who had received a course of radiotherapy were reviewed. The mean age was 67.7 years (range 35–85); 48 patients were male and 5 female; 46 patients presented with a G3pT1 tumour, whereas 7 had previously been treated by endoscopic resection for a more differentiated cancer (2 were G1pT1 and 5 were G2pT1). All patients were followed up for a minimum of 1 year or until death.

All patients were initially diagnosed and treated by transurethral resection and subsequently given a course of radical irradiation administered to the bladder only (usually with the 5 or 8 meV linear accelerator) at a dose of 5000 to 5500 cGy in 20 fractions over 4 weeks (Hope-Stone, 1986). Cystoscopy was performed 3 and 6 months after completion of the course of radiotherapy. If poorly differentiated tumour persisted at 6 months, or recurred later, or if the tumour became invasive, patients were offered a salvage cystectomy if they were medically fit and without distant metastases. Patients showing tumour regression were followed by 3-monthly cystoscopies for 2 years and 6-monthly thereafter.

Survival curves were calculated by the actuarial method: all patients without clinical evidence of tumour for more than 1 year and whose death had a non-malignant cause unrelated to treatment were censored at death (Barnes, 1965).

Based on a Poster Demonstration at the 43rd Annual Meeting of the British Association of Urological Surgeons in Edinburgh, July 1987

Results

The overall corrected 5-year survival rate of these 53 patients was 64% (Fig.).

Response to radiotherapy

Forty of 53 patients (75%) showed an initial complete response to radiotherapy; 13 (25%) failed to respond and progressed to develop an invasive tumour. Six of these patients underwent cystectomy and all did well initially but 1 died with metastases 3 years later. Seven patients who developed an invasive cancer were not offered a cystectomy: in 3 of these patients distant metastases were evident within a few months of presentation and 4 were considered unfit.

Carcinoma in situ

Ten patients developed secondary carcinoma *in situ* (pTis) (UICC, 1978) between 6 and 18 months (mean 9) after the course of radiotherapy. They were treated with intravesical chemotherapy—either Mitomycin C (30 mg/week for 6 weeks) or thiotepa (30 mg on alternate days for 3 doses); 4 of these patients subsequently developed an invasive tumour.

Discussion

Patients with G3pT1 bladder cancer treated by transurethral resection alone have a poor prognosis: 50% are likely to develop an invasive tumour and only 20% are alive at 5 years (Pocock *et al.*, 1982; Heney *et al.*, 1983; Jakse *et al.*, 1987; Abel *et al.*, 1988). The 25% incidence of subsequent muscle invasion and 64% 5-year survival rate in this series support the findings from Edinburgh, where 55.6% of patients treated with radiotherapy for G3pT1 disease showed no recurrence at 5 years and none developed either local or distant disease between 5 and 10 years after radiotherapy (Quilty and Duncan, 1986).

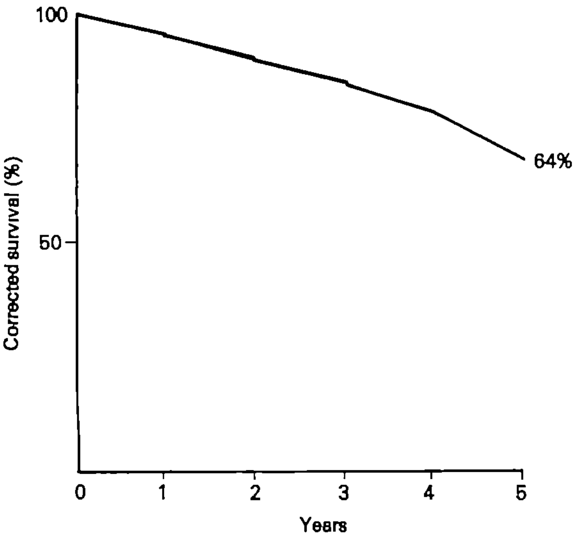

Fig. Survival of 53 patients with G3pT1 bladder cancer treated by radical radiotherapy.

The presence of carcinoma *in situ* is known to have an adverse effect on the prognosis of superficial bladder cancer (Althausen *et al.*, 1976). In this series, 4 of 10 patients with a G3pT1 tumour and carcinoma *in situ* went on to develop an invasive cancer despite radical radiotherapy and intravesical chemotherapy.

The blanket term 'superficial' can conceal this dangerous group of tumours. G3 cancers are potentially lethal and should be treated as such.

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Structure and Per-rectal Ultrasonography of Prostatic Disease using Cadaver Specimens

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Summary—One hundred cadaver prostates were examined by per-rectal ultrasound and the findings correlated with the microradiographic and histopathological features of whole sections taken at the levels of scanning.

The normal gland consists of both periurethral muscle and glands. The periurethral muscle has little structure on microradiography and is therefore hypoechoic (low amplitude echoes) on ultrasound scanning. The gland itself, both central and peripheral zones, has a lattice appearance on microradiography (reticular structure) and therefore produces mid-range amplitude echoes on ultrasound.

Benign hypertrophy develops at the edge of the periurethral muscle and is microadenomatous in structure. This produces mid-range amplitude echoes which are coarser than in the normal gland. Associated calcification has a characteristic distribution around the adenomas.

Cancer produces an amorphous structure resulting in loss of ultrasonic echoes (hypoechoic). In a few cancers irregular calcification is present, resulting in high echoes in the ultrasound scan (hyperechoic) which are not in the typical benign distribution.

The internal structure of the prostate was therefore demonstrated in its histopathological states by the technique of microradiography and seen to relate to its representation by ultrasound.

The exact representation of prostatic disease by per-rectal ultrasonography and its mechanism is controversial. Cancer has been described as focally dense asymmetrical areas (Resnick *et al.*, 1978) and other workers have described it as hyperechoic on ultrasound scanning (Watanabe *et al.*, 1975; Harada *et al.*, 1980; Rifkin *et al.*, 1983). Further studies suggested that cancer was heterogeneous (Peeling *et al.*, 1979, 1984, 1987).

Lee *et al.* (1985) described cancer as represented by hypoechoic areas in the prostate. They noted that all of the carcinomas had originated in the peripheral zone. In 1986 they described a biopsy technique proving that hypoechoic areas were the site of cancers.

The ultrasonic appearances of prostatic cancer with histopathological correlation have been investigated by Griffiths *et al.* (1987); 92% were found to be hypoechoic, 2% hyperechoic and 6% isoechoic (no change in echogenicity). Dahnert *et al.* (1986) described ultrasonic examination of excised prostates in a water bath; 54% were found to be hypoechoic, 22% slightly hypoechoic and 24% isoechoic.

The percentage of cancers that are hyperechoic, isoechoic and hypoechoic is therefore debatable but evidence exists that all occur and it is necessary to attempt to explain the different types of echoes found in prostatic cancer.

Correlation of ultrasound scans with the histopathology of whole prostates has been suggested as a means of understanding the ultrasonic findings in

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various diseases of the prostate gland (Rifkin *et al.*, 1986). Analysis with corresponding microradiographs will explain the mechanism of the ultrasonic features and such a technique has now been developed (Davies *et al.*, 1988).

Materials and Methods

Comparative histopathological, microradiographic and per-rectal ultrasound sections from 100 cadaver specimens were examined. Of these, 87 were "random" specimens and 13 were from patients known to have cancer of the prostate. Legal and ethical permission was obtained. The patients' ages ranged from 17 to 90 years (mean 63).

The prostate, bladder, rectum and anus were taken within 48 h of death and suspended in a perspex tank so that per-rectal ultrasound examination could be performed. The prostates were then dissected and fixed, after which complete transverse sections were cut at the levels of scanning for histopathological and microradiographic analysis.

The different histopathological findings were compared with the structure, as shown in the microradiographs and ultrasound echogenicity in corresponding areas of the glands (Jones *et al.*, 1989).

Results

Benign prostatic hyperplasia and its development

Benign hyperplasia is seen on microradiography to develop at the periphery of the periurethral muscle (Fig. 1). It consists of small rounded masses ("microadenoma") aggregated together to make larger masses ("macroadenoma") (Fig. 2A). There is obliteration of the muscle/gland boundary on ultrasonography with coarser mid-range echoes (Fig. 2B). The structure of these adenomas is thicker than that of the "reticular" non-diseased glands.

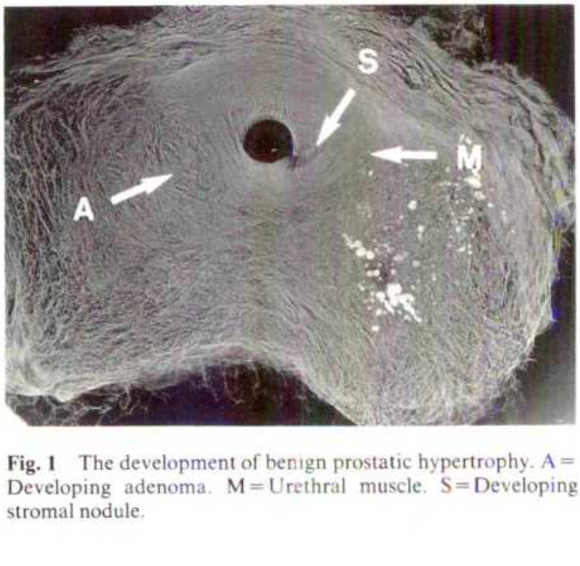

Fig. 1 The development of benign prostatic hypertrophy. A = Developing adenoma. M = Urethral muscle. S = Developing stromal nodule.

Stromal nodules

Some nodules are seen to develop within the urethral muscle, initially expanding it (Fig. 1). When larger they are in very close proximity to the urethral lumen and on microscopy are seen to be stromal nodules. Microradiography shows them to be completely regular and amorphous in structure (Fig. 3A). These lesions tend to be hypoechoic on ultrasonography, consistent with their structure (Fig. 3B).

Stromal nodules, therefore, have a different structure and origin from the more common "microadenomatous" type of benign hyperplasia.

Calcification and benign disease

Calcification is a common feature in the prostate gland. In benign conditions it is seen to have a distinct distribution (Figs 2A and B). The calcifications are rounded and regular in nature and are present in the urethral ducts, main prostatic ducts or distributed around benign adenomas, with peripheral prostate more superficial. The ultrasound scans show the calcification as distinct, very high echoes in a "W" distribution in the gland. The peripheral zone of the prostate is seen around it on ultrasound—a feature of calcification associated with benign disease.

Cancer of the Prostate

Twenty-nine prostates had cancer present, of which 16 were incidental findings; the remaining 13 were known to be malignant before death.

Involvement of the prostate by cancer is seen on microradiography to distort and destroy the benign structure of the gland (Fig. 4A). Localised cancers produce low echo areas on ultrasonography (Fig. 4B) related to the loss of benign structure. The original structure can become partly or completely destroyed and amorphous (Fig. 5A) with little or no echoes on ultrasound (Fig. 5B).

Note has been made of lower echoes in unconfined cancers compared with confined or the same cancer inside the gland. This study has shown that some unconfined cancers have not completely destroyed the original structure of the gland. In these cases some echoes were produced from the

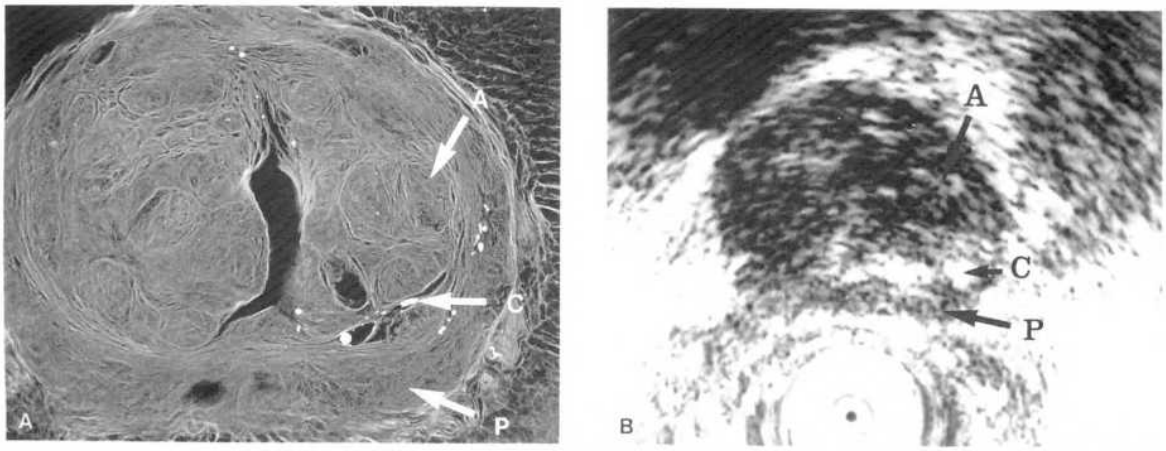

Fig. 2 Developed benign prostatic hypertrophy. (A) Microradiograph. (B) Ultrasound. C = Calcification around adenoma. A = Adenoma. P = Peripheral Zone.

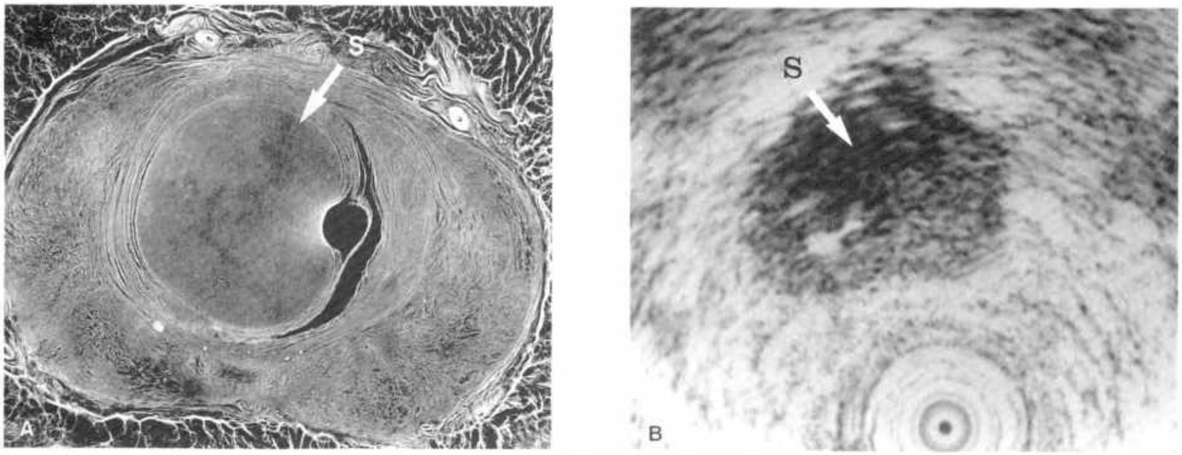

Fig. 3 Stromal nodule. (A) Microradiograph. (B) Ultrasound. S = Stromal nodule (intimately related to the urethra). Rest of gland reticular in structure.

gland, whereas the cancer outside the gland was hypoechoic where only amorphous structure was present.

Echogenicity of cancers (Tables 1 and 2)

A) Hypoechoic cancer. Most cancers (19) were represented ultrasonically as hypoechoic areas. In these cases the microradiographs show amorphous architecture with no calcification present in the tumour. The loss of structure and tissue surfaces explains the decrease in ultrasonic echoes (Figs 4 and 5).

B) Isoechoic cancer. Four cancers had no changes on ultrasonography. Microradiographs of these areas show no change in the structure of the gland (Fig. 6A), which explains the absence of changes on ultrasonography (Fig. 6B). All were confined cancers, being 0.5 cm or less in diameter and so too small or "not malignant enough" to cause structural changes.

C) Hyperechoic cancer. Six cancers were represented on ultrasound by high echoes. Microradiographs of these areas again showed loss of structure but in addition there were areas of irregular shaped calcifications within the cancers (Fig. 7A). These calcifications were distributed randomly in and around the cancers and quite unlike the regular calcifications as described in association with

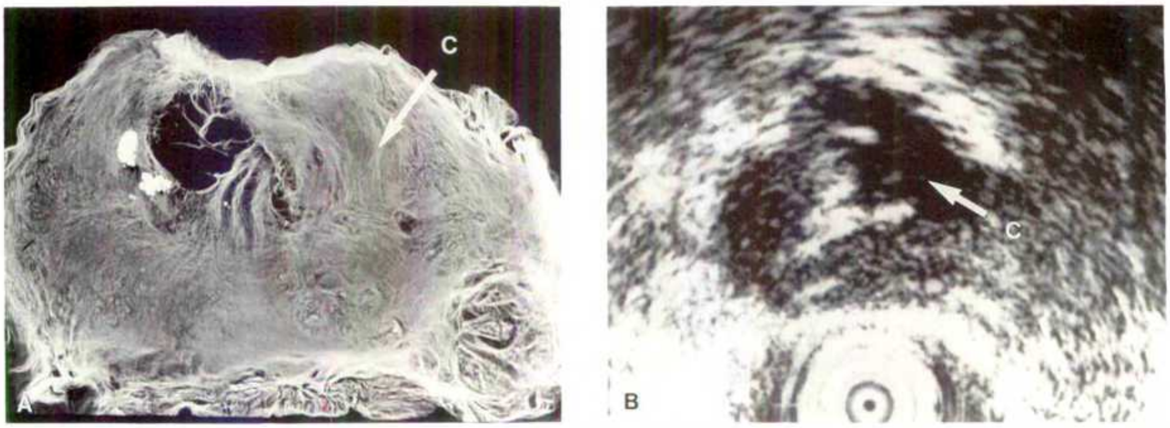

Fig. 4 Cancer: hypoechoic (confined). (A) Microradiograph. (B) Ultrasound. C = Cancer (localised). Loss of benign structure with distortion. Rest of gland: mid-range echoes.

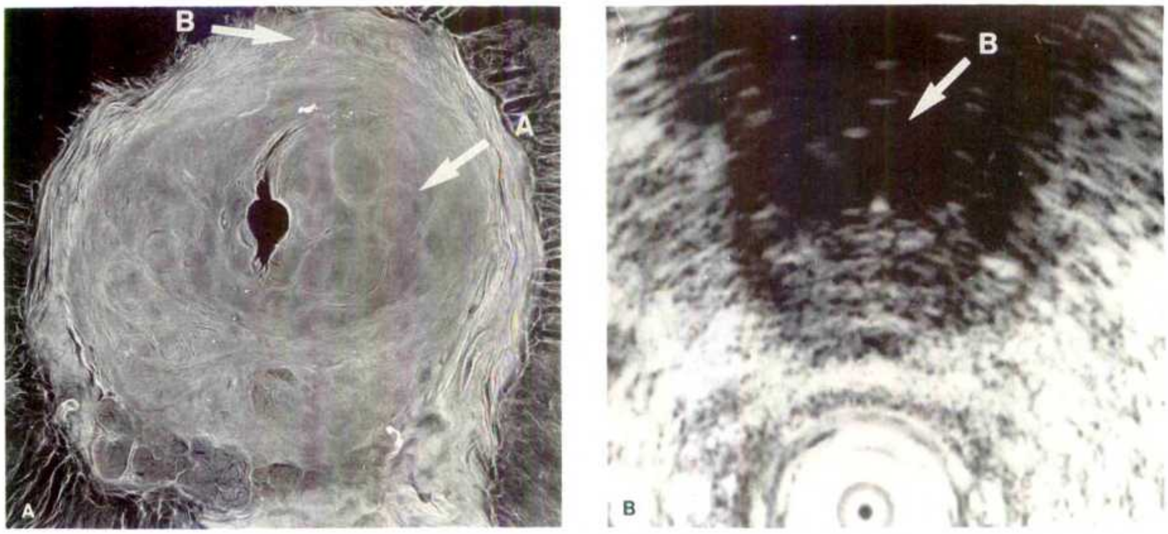

Fig. 5 Cancer: hypoechoic (unconfined). (A) Microradiograph. (B) Ultrasound. B = Breached capsule. A = Loss of fine structure. Some gross nodular stucture remaining, resulting in some echoes.

benign disease. This association of calcification with some cancers explains the hyperechoic areas on ultrasonography (Fig. 7B).

No other structural change was seen to account for the increased echoes in these cases of cancer, as seen on microradiography or the histopathological sections. In particular there was no evidence to indicate increased collagen in association with tumours, as suggested by Greenberg *et al.* (1981).

Differentiation of calcification associated with benign and malignant disease

Since calcification occurs in association with both benign and malignant disease, it is important to differentiate between the two. Microradiography has shown differences in shape and distribution between the 2 types of calcification and this is reflected in the corresponding ultrasonic scans. "Benign" calcification has a rim of prostate around it on ultrasound scans but this is not present in the case of malignant calcification. This appears to be a differentiating feature. Malignant calcification often appeared as areas containing multiple high echoes, whereas "benign" calcifications appear in a "W" distribution.

It is probable that previous reports indicating

Table 1 Echogenicity of the Cancers (N = 29)

Echogenicity	*No. (%)*	*Calcification*	*Structure*
Hypoechoic	19 (66)	No calcification in tumour	Amorphous
Isoechoic	4 (14)	Calcification when present in benign distribution	Structured (No structural change present)
Hyperechoic	6 (20)	Calcification in tumour	Amorphous

Table 2 Echogenicity of Confined and Unconfined Cancers

Echogenicity	*Confined (N = 16) No.*	*%*	*Unconfined (N = 13) No.*	*%*
Hypoechoic	7	44	12	93
Isoechoic	4	25	0	0
Hyperechoic	5	31	1	7

that there was no association between prostatic calcification and malignancy resulted from failure to differentiate between the 2 types of calcification.

The capsule and periprostatic tissue/staging of prostatic cancer

The imaging of the prostatic capsule is important, particularly in regard to the staging of prostatic cancer. Histopathological studies have shown that the capsule is an ill-defined layer of fibromuscular tissue separating the glandular elements from the surrounding adipose tissue and fat. The latter, as elsewhere, produces high echoes on ultrasonography. The ultrasonic boundary of the prostate is therefore between the glandular and adipose tissue.

(A) Confined cancer. All 16 confined cancers were correctly staged on ultrasonography. The cancers that did not involve the periprostatic fat appeared confined on ultrasonography. Of the 16 confined cancers, 4 involved the capsule (not penetrating it) and 12 were within the gland. Involvement only of the capsule without penetration or involvement of fat caused the tumour to appear confined on ultrasonography.

(B) Unconfined cancer. The cancers involving the periprostatic fat appeared as unconfined on the ultrasound scan with loss of the ultrasound boundary. Twelve of the 13 unconfined cancers were correctly staged.

Discussion

Diseases of the prostate gland and their structural and ultrasonic features have been studied in 100 cadaveric prostates.

Benign prostatic adenomas develop at the lateral margin of the periurethral muscle (the transitional zone) and obliterate the ultrasonic boundary nor-

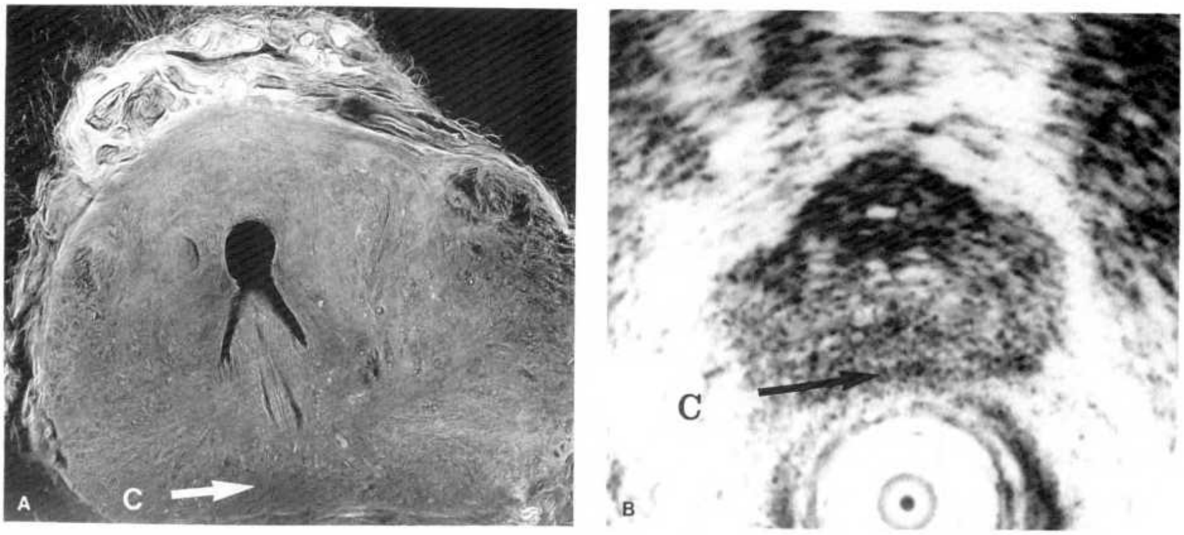

Fig. 6 Cancer: isoechoic. (A) Microradiograph. (B) Ultrasound. C = Cancer (small). No structural or ultrasonic change.

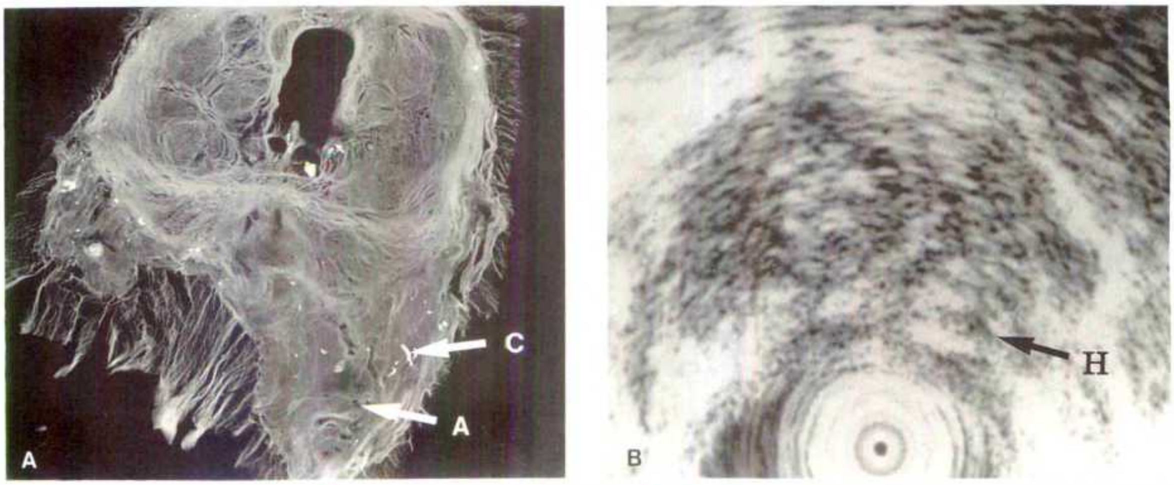

Fig. 7 Cancer: hyperechoic. (A) Microradiograph. (B) Ultrasound. H = High echoes with distortion. C = Irregular calcification in tumour. A = Amorphous mass.

mally present. These tumours consist of an aggregation of smaller rounded lesions resulting in coarser mid-range echoes ultrasonically. Stromal nodules have a different structure (amorphous) and develop inside the periurethral muscle. They produce low ultrasonic echoes.

Cancer is commonly represented as hypoechoic areas, although isoechoic and hyperechoic areas also occur. Cancer produces amorphous structuring of the gland, destroying the normal benign appearance. This results in hypoechoic areas on ultrasonography. Hyperechoic cancers are associated with irregular calcification in the amorphous tumours, which explains the change in echogenicity and can be differentiated from benign calcification on ultrasound. The isoechoic cancers are small confined lesions which have not produced structural change in the gland (25% of confined cancers and less than 0.5 cm in diameter).

The echogenicity of the prostate gland on ultrasonography is therefore related to its internal structure and this is determined by the pathological processes that are present.

Per-rectal ultrasound is an accurate method of staging prostatic cancer. "Malignant' breach of the ultrasonic capsule of the prostate gland is related to involvement of the periprostatic fat by the tumour and not just involvement of the true prostate capsule.

Acknowledgements

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Bladder Outflow Tract Obstruction and Urinary Retention from Benign Prostatic Hypertrophy Treated by Balloon Dilatation

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Summary—Forty-eight men with urodynamically proven bladder outflow tract obstruction (BOO) and 19 with retention secondary to benign prostatic hypertrophy were treated by balloon dilatation of the prostate as out-patients; 31 were dilated with 20 mm and 36 with 25 mm balloons. Of the 48 men with BOO, 37 had repeat cystometrograms at intervals ranging from 3 to 11 months after dilatation and 33 (89%) remained obstructed by urodynamic criteria. Of 6 who only had a peak flow rate assessment, 5 had a flow < 12 ml/s. Of the 19 patients in retention only 3 were able to void and all are obstructed. Symptoms of hesitancy, poor stream, frequency and nocturia were improved in less than 50% of patients. No reliable correlation was found between objective response and balloon size, length of time of dilatation, prostate size or morphology, detrusor pressure or stability, or post-dilatation urethrogram appearances. Balloon dilatation to 25 mm is not adequate therapy for bladder outflow tract obstruction or urinary retention from prostatic hypertrophy.

Bladder outflow tract obstruction secondary to benign prostatic hypertrophy is the commonest disorder to affect men over the age of 50 (NIHCC, 1978). Current optimal therapy is transurethral resection of the prostate (TURP), with 34,630 prostatectomies performed in the United Kingdom in 1985 (DHSS, 1987). However, TURP is associated with a mortality rate of up to 6.4% in selected high risk groups (Melchior *et al.*, 1974) and 15% of patients will have complications that include impotence, retrograde ejaculation, urethral strictures, haemorrhage, incontinence, epididymitis and urinary extravasation. In addition, 16.8% of patients will require re-operation within 8 years of the original procedure (Roos and Ramsay, 1987).

Balloon dilatation of the prostate was first described by Burhenne *et al.* (1984) but to our knowledge no large series of patients with objective evidence of bladder outflow tract obstruction and cystometrographic follow-up has been reported. This study was performed to determine the safety and efficacy of balloon dilatation of the prostate in the treatment of patients with objective evidence of bladder outflow tract obstruction or urinary retention.

Patients and Methods

A series of 119 patients with a diagnosis of "prostatism" and 19 patients presenting in retention (12 in acute and 7 in chronic retention) were studied All had peak urinary flow assessment and a cystometrogram; 85 patients with a urethral resistance factor of 0.6 or more were considered to have significant bladder outflow tract obstruction (Abrams *et al.*, 1983); 48 of these patients and the 19 patients in retention accepted the option of balloon dilatation of the prostate.

Each patient had a physical examination by a member of the Urology Department, and full blood count, blood urea and electrolytes. Blood and urine cultures were obtained. Piperacillin 2 g was given intravenously prior to the procedure. In the Radiology Department, using fentanyl and diazemuls sedation, a retrograde urethrogram was performed to define the external sphincter (Fig. 1).

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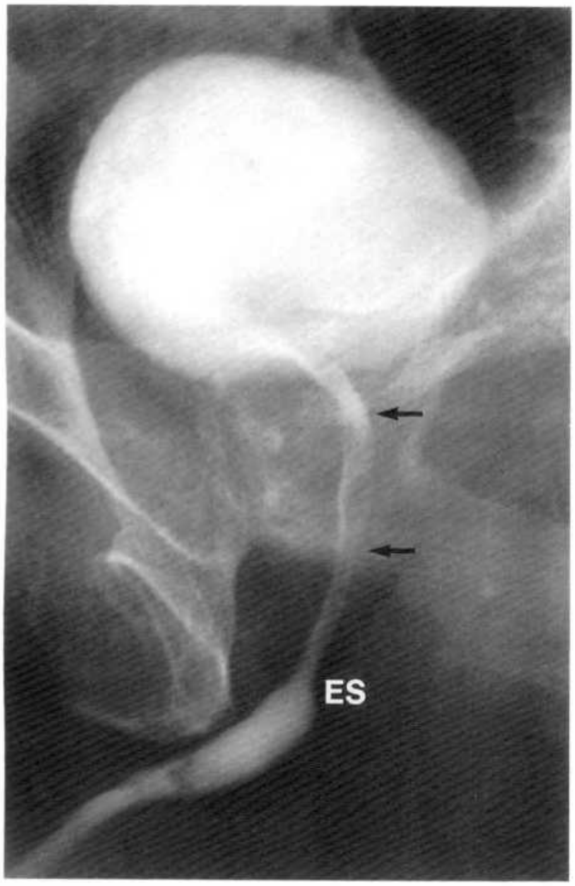

Fig. 1 Retrograde urethrogram before dilatation. The external sphincter is marked (arrow).

The bladder was catheterised with an 8 F steerable catheter and this was exchanged over an 0.038 inch guidewire for a balloon dilatation catheter which was then inflated under radiological control (Fig. 2), taking particular care to avoid the external sphincter. The first 31 patients were dilated with a 20 mm oesophageal dilatation balloon (Meditech Inc., Watertown, USA) and the subsequent 36 with a 25 mm diameter, 5 cm long prostatic urethroplasty balloon (Meditech Inc.). The balloon was inflated for 6 min in the initial 15 patients and for 15 min in the remainder. At the end of the procedure, a 16 gauge Foley catheter was inserted and the patient was observed for 1 h before being discharged home.

After 24 h the patient returned to the Radiology Department, the Foley catheter was removed and a retrograde urethrogram was performed. Patients in retention who did not void following dilatation were offered the option of a repeat dilatation or TURP; 15 patients had a repeat dilatation. Clinical follow-up included measurement of flow rate and bladder residual urine, and completion of symptom charts 24 hours, 2 weeks, 3 months, 6 months and 1 year after treatment. However, as the study evolved, although the patients were seen at the same intervals, it became apparent that it was not ethical to follow up all patients for 1 year.

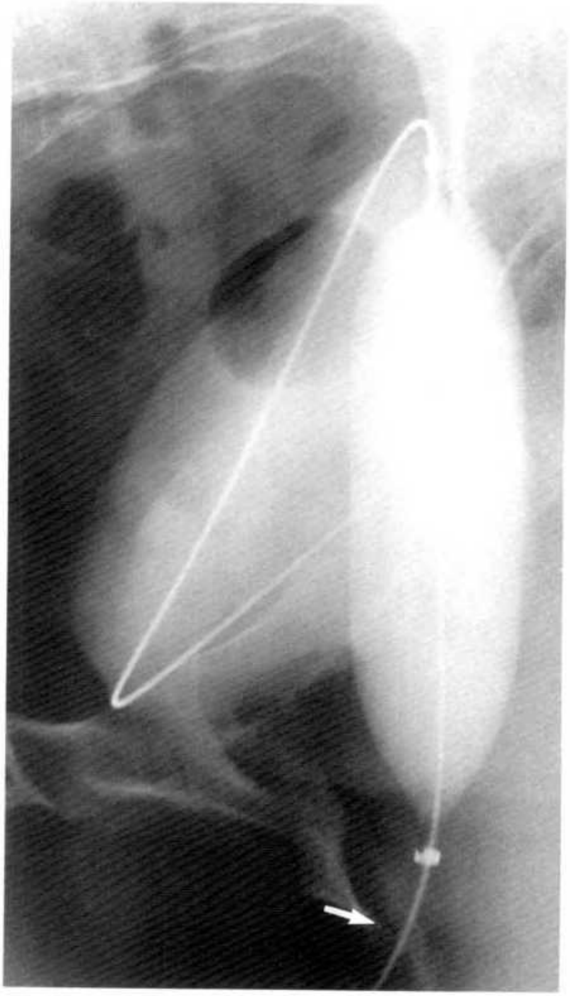

Fig. 2 Inflated balloon in prostatic urethra. Proximal aspect of the balloon is above the level of the external sphincter (arrow).

Thirty-seven of the 48 patients with BOO had a repeat cystometrogram at intervals from 3 to 11 months after treatment and 6 had a peak flow rate assessment.

Results

Of the 37 patients treated by balloon dilatation who had follow-up CMGs, only 4 (11%) were not

Table Patients Responding to Balloon Dilatation

No. of patients	*Urethral resistance factor*		*Balloon diameter (mm)*	*Duration of dilatation (min)*	*Split urethra*	*Detrusor*
	Before dilatation	*after dilatation*				
1	1.1	0.28	20	6	No	Stable
2	8.3	0.43	20	15	No	Stable
3	1.6	0.55	25	15	No	Unstable
4	1.9	0.1	25	15	Yes	Unstable

obstructed by urodynamic criteria. Of the 6 patients who did not have subsequent CMGs and were not lost to follow-up, 1 had a flow rate >12ml/s 3 and 6 months after treatment but the other 5 had flow rates <12 ml/s at 3 months. A summary of patients responding to balloon dilatation is presented in the Table. In comparison with the appearance of the pre-dilatation urethrogram, the post-dilatation retrograde urethrogram was unchanged in 3 of the patients who responded to dilatation, and a definite splitting of the prostatic urethra was seen in the other. Overall, the urethra was unchanged after dilatation in 23 patients (48%) and was split in 25 patients (52%) (Fig. 3). Two of the patients who responded to dilatation had no significant intravesical prostatic component and 2 had a moderate-sized median lobe.

Two of the 4 patients responding to therapy reported no improvement in symptoms of hesitancy, poor stream or daytime frequency. Both had

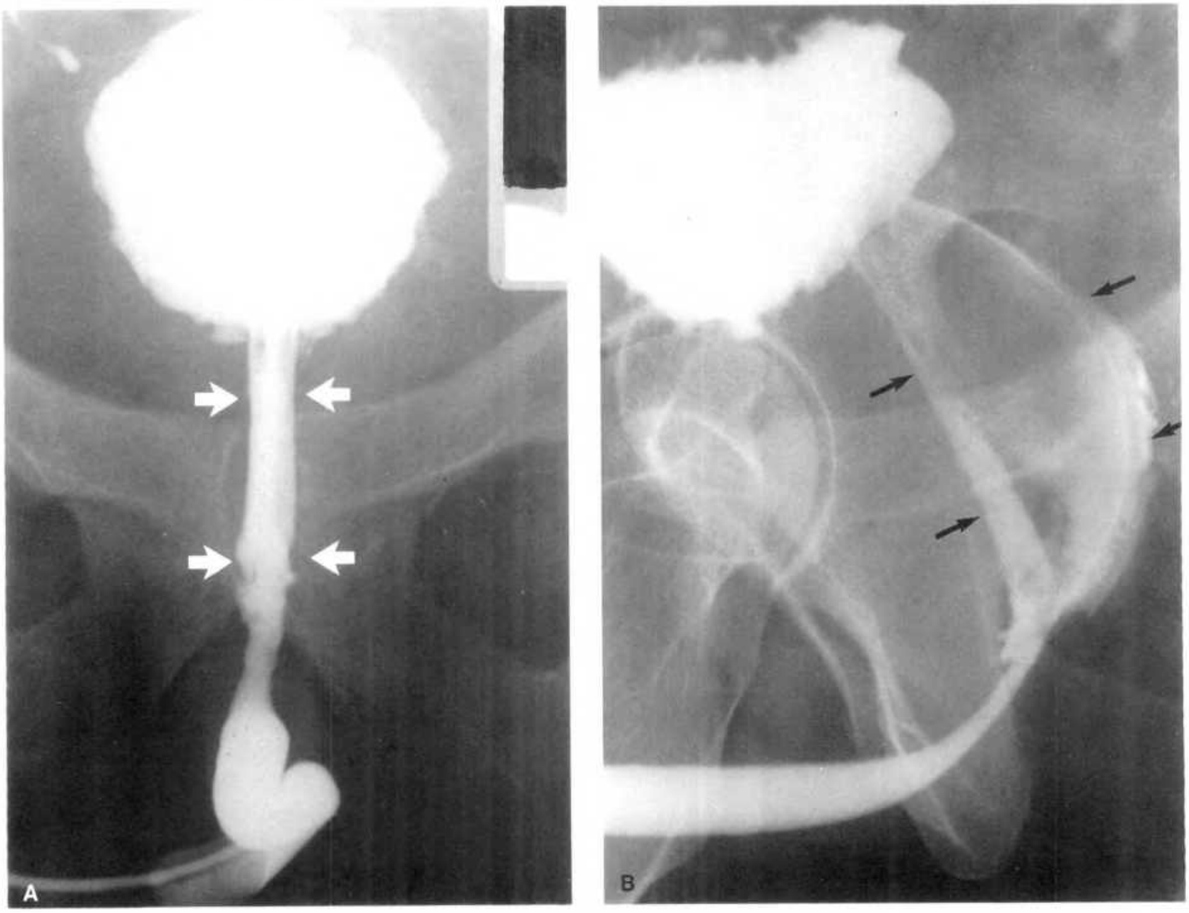

Fig. 3 Retrograde urethrogram after dilatation in AP projection (A) and oblique projection (B). A prostatic commissurotomy has been performed.

unstable detrusors at urodynamic assessment both before and after dilatation.

The other 2 responding patients reported an improvement in symptoms of hesitancy, poor stream and daytime frequency; 1 had a stable detrusor and the other an unstable detrusor on CMG before and after dilatation. All 4 patients responding to balloon dilatation noticed decreased nocturia but 2 of the 4 had reduced their evening fluid intake after treatment.

Forty-three of the 48 patients presenting with bladder outlet obstruction completed symptom charts 3 months after treatment; 11 (26%) felt there was a good improvement in stream, 7 (16%) a moderate improvement and 25 (57%) felt their stream was unchanged or worsened. In comparison with pre-dilatation symptoms, at 3 months 13 of 43 patients (30%) reported decreased daytime urinary frequency, 15 (35%) reported worsening daytime frequency and 15 (35%) felt there was no change.

Twenty-one of 43 patients (49%) reported diminished nocturia, although the changes were frequently slight and the mean frequency of nocturnal voiding was 3.3 times before dilatation (range 0–8) and 2.6 times 3 months after dilatation (range 0–6); 29 of 48 men (60%) were arising more than twice a night before dilatation and 21 of 43 (48%) were getting up more than twice a night 3 months after dilatation. Of the 21 patients who had decreased nocturia, 4 had reduced their night-time fluid intake following dilatation.

The mean prostatic volume assessed by transrectal ultrasound of the 4 patients who responded to dilatation was 57 ml (range 40–70). This compared to an overall mean prostatic volume of 69 ml (range 40–117).

Of the 12 patients presenting in acute retention, 2 are voiding but are obstructed on CMG. Two further patients initially voided following repeat dilatation but 1 subsequently went into retention and the other is urodynamically obstructed.

Of the 7 patients presenting in chronic retention, 1 voided after repeat dilatation and had a flow rate of 8 ml/s at 2 weeks. He did not attend for follow-up CMG.

Complications were minimal. Nine patients (13%), 4 of whom had indwelling catheters, suffered uncomplicated urinary tract infections which responded to oral antibiotics. All patients developed haematuria, which in most cases resolved in less than 24 h. Four patients had more significant haematuria requiring the Foley catheter to be left in for a further 24 h.

Two patients died, 1 patient presenting in chronic retention, from pneumonia 2 weeks after dilatation. There was no evidence of urinary sepsis at autopsy. The second patient, who presented with BOO, died of bronchopneumonia 5 months after dilatation.

Discussion

Deisting (1956) reported that mechanical stretching of the prostatic urethra with metallic dilators in 324 patients produced an 84.8% success rate as indicated by residual urine measurement at 8 years. However, other authors were unable to duplicate his findings at 1 year (Backman, 1963) or at 5- and 10-year follow-up (Sandberg and Sandstrom, 1967). Castaneda *et al.* (1988a) reported a 75% success rate for balloon dilatation to 25 mm in the treatment of "prostatism" in patients with lateral lobe hypertrophy only. The success rate dropped to 25% when the patient had significant median lobe hypertrophy. However, none of these patients was reported to have had urodynamic evaluation before or after the procedure, and success was decided by symptoms alone. In this study, 26% of patients presenting with symptoms of bladder outflow tract obstruction did not meet urodynamic criteria for obstruction and were not treated by this technique.

Of 42 patients with large or moderate sized median lobes, only 1 (2%) responded to dilatation, and only 3 of 25 (12%) with small or no median lobe extending intravesically responded in this series.

It has been suggested that the mechanism of action of balloon dilatation is splitting of the commissures of the prostate (Fig. 3) and some authors advocate using this as the end point of dilatation rather than choosing a specific length of time (Castaneda *et al.*, 1988b). Operative commissurotomy has been reported to have a 91% success rate (Shafik, 1986). Twenty-three of the dilatations performed in this study did not result in splitting of the prostate by retrograde urethrographic criteria (*i.e.* there was no change in comparison to pre-dilatation appearances), but 3 of the 4 patients who responded were among these 23 patients. Cystoscopic examination immediately after dilatation revealed no significant change in the prostatic urethra apart from stretching of the bladder neck.

The technique of performing balloon dilatation is an important consideration. In all cases the balloon was inflated until there was no evidence of a waist. Great care was taken to avoid dilating the external sphincter. It was important to maintain traction on the catheter during the dilatation, maintaining the balloon within the prostatic urethra, as it tended to propel itself forcibly into the bladder, particularly during inflation.

Once the inflated balloon had been allowed to advance into the bladder, attempting to replace it in the prostatic urethra with the balloon fully inflated resulted merely in descent of the pelvic floor and not its insertion into the prostatic urethra. We have demonstrated this both by transrectal ultrasound during the procedure and by marking the position of the external sphincter by instilling contrast through a 5 F catheter placed alongside the dilatation catheter in the penile urethra.

In this unselected patient population, only 6% responded to balloon dilatation of the prostate. It has been suggested that the most suitable patient is one with a small prostate and lateral lobe hypertrophy alone. Even when these variables are taken into consideration, balloon dilatation was ineffectual in the majority of cases. We have also found no reliable correlation between response and detrusor pressure or stability, dilatation time, balloon size or post-dilatation appearance of the retrograde urethrogram.

Although we have shown that balloon dilatation of the prostatic urethra to 25 mm is a safe procedure, urodynamic and symptomatic assessment of patients lead us to conclude that it is not an effective treatment for bladder outflow tract obstruction.

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Transurethral Resection of the Prostate and Bladder Tumour without Withdrawal of Warfarin Therapy

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Summary—Twelve resections of prostate and 1 extensive bladder tumour were performed in patients on long-term anticoagulation without withdrawal of warfarin therapy. The mean pre-operative prothrombin index was 2.3. Four patients required blood transfusion. There were no major complications.

The effects of surgery and infusion of fresh frozen plasma (FFP) on the level of anticoagulation were monitored. FFP reduced the prothrombin index by 0.25/unit. Transurethral resection can be carried out safely by an experienced urologist on patients anticoagulated with warfarin, reducing the risk of serious thromboembolic complications associated with withdrawal of anticoagulation.

When elective surgery is performed on patients receiving long-term anticoagulant treatment, it is usual practice to discontinue therapy over the peri-operative period (Mulcahy *et al.*, 1975). Although various authors have demonstrated that the risks of thromboembolic complications can be reduced by the use of low dose subcutaneous heparin (Kakkar *et al.*, 1971; Sagar *et al.*, 1975) or antiplatelet drugs (Sullivan *et al.*, 1971), it is questionable whether these agents alone provide adequate prophylaxis in patients who normally require to be fully anticoagulated. More recently Tscholl *et al.* (1980) demonstrated it was safe to perform electroresection of the prostate on patients fully anticoagulated with heparin.

The Mersey Regional Cardiothoracic Centre is situated at Broadgreen Hospital and it is quite common for patients who are anticoagulated with warfarin to be referred to the urology department. Since 1982, all transurethral resections have been carried out with uninterrupted warfarin therapy. The results of this policy have been reviewed.

Patients and Methods

Since 1982, 14 patients have undergone significant endoscopic resections without withdrawal of warfarin therapy; 13 transurethral prostatectomies and 1 transurethral resection of an extensive bladder tumour were performed. One patient was subsequently excluded from the review as his pre-operative level of anticoagulation was deemed inadequate (prothrombin index < 1.5). The remaining 13 patients were aged 57 to 75 years (mean 67). The indications for anticoagulation are listed in the Table. Eight patients presented with acute or chronic retention, 4 had symptoms of outflow obstruction and the patient with a bladder tumour presented with haematuria. All surgery except for 1 case was performed by a consultant urologist (ADD). All resections were carried out under general anaesthesia using a continuous irrigating resectoscope. Haemostasis at the end of the resection was achieved by diathermy coagulation using a ball electrode, a 22F plastic irrigating catheter for bladder drainage and digital pressure *per rectum* on the prostatic capsule combined with suprapubic

Table Indications for Anticoagulation

Venous thrombosis (5)
Heart valve prostheses (2)
Coronary artery bypass surgery (3)
Transient ischaemic attacks (1)
Ventricular aneurysm (1)
Endocardial thrombosis (1)

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manual pressure (Freyer, 1901). Continuous bladder irrigation was maintained for approximately 24 h after surgery.

Results

Pre-operative haemoglobin levels ranged from 10.9 to 19.7 g/dl with a mean of 14.1 g/dl (Fig. 1). Four patients required blood transfusion (2,2,2,4 units) over the peri-operative period, 3 of whom were also given 2 units of fresh frozen plasma. Post-resection haemoglobin levels measured on the first or second post-operative days ranged from 10.2 to 18.3 g/dl (mean 12.8).

The mean pre-operative prothrombin index was 2.3, ranging from 1.6 to 2.8 (Fig. 2). In 6 patients, a more detailed assessment was made of any change in prothrombin levels resulting from the operative procedure and infusion of FFP. The prothrombin index was monitored before, during and/or immediately after the procedure. There was no significant change in level (Fig. 2). In 2 of these cases, FFP was infused at the end of the operation (3,4 units) and the prothrombin index measured for 24 h. This resulted in a sharp drop in prothrombin index at 30 min which was maintained for the next 2 to 3 h. The level had risen by 24 h in the patient given 3 units of FFP but remained depressed in the patient given 4 units (Fig. 3).

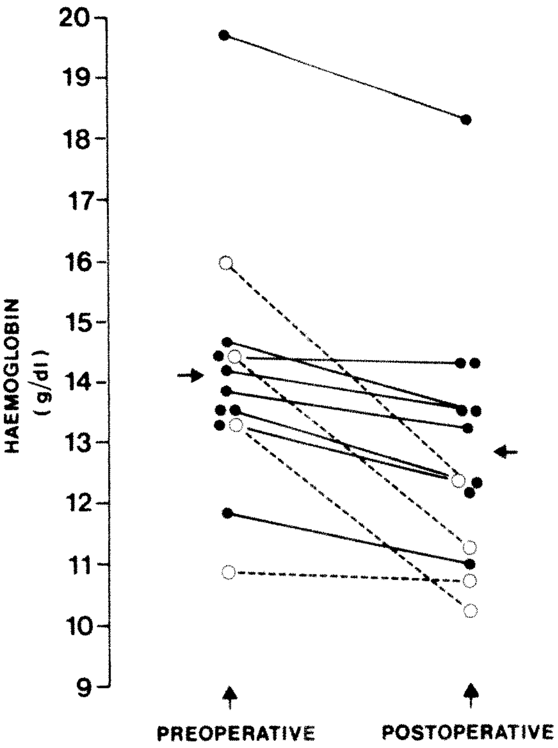

Fig. 1 Haemoglobin levels before and after resection. Dotted line indicates patients who received blood transfusion. (→ ← denotes mean levels).

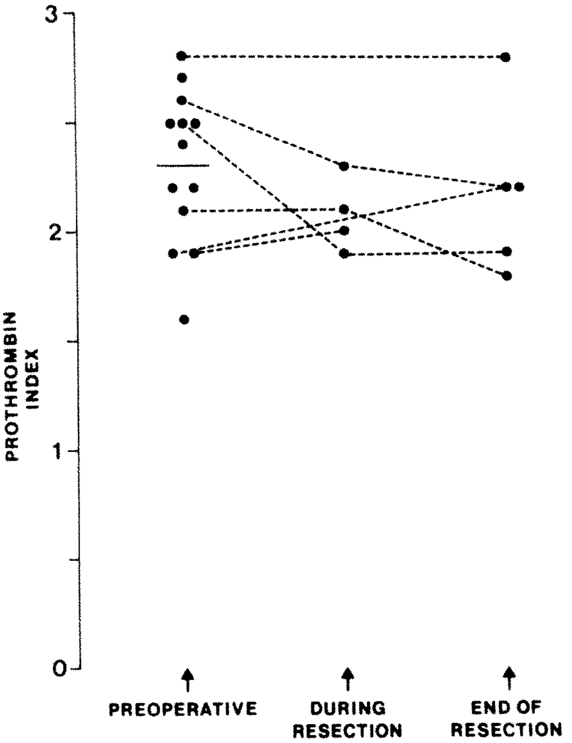

Fig. 2 Pre-operative prothrombin levels (— depicting mean). Effect of resection alone in 6 patients on per and/or post-operative levels.

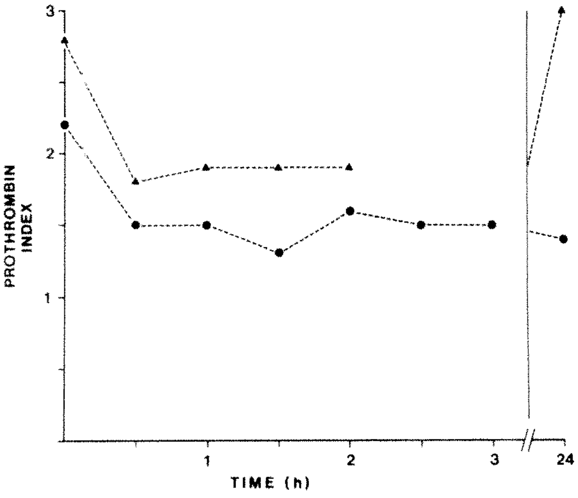

Fig. 3 Effect of infusion of FFP after resection on prothrombin index (▲ 3 units, ● 4 units).

The mean weight of tissue resected was 22 g (range 6–41); 3 of the prostates were malignant, the remainder demonstrating benign hypertrophy. The bladder tumour was an extensive superficial transitional cell carcinoma (37 g) classified G2 pT1. Six patients had their catheters removed by day 2, 9 by day 3 and 13 by day 5. One patient developed clot retention requiring recatheterisation until day 8. There were no other complications.

Discussion

The rationale of stopping anticoagulation therapy prior to surgery is to reduce the presumed risk of increased haemorrhage. The main factors limiting blood loss during transurethral resection are the use of hypotensive anaesthesia (Bruce *et al.*, 1960), small vessel vasoconstriction and diathermy coagulation, none of which is affected by the action of warfarin. However, the inhibitory action of warfarin on the clotting mechanisms should influence capillary and venous haemostasis. Theoretically this might lead to a prolongation of post-operative haemorrhage. Except in 1 case, this was not apparent.

The use of FFP to control bleeding is well known, but its use for selectively reversing the anticoagulant effect of warfarin has not been widely documented in the surgical literature. During transurethral prostatectomy, we have shown that FFP can effectively, rapidly and temporarily reduce the prothrombin index at the rate of approximately 0.25 per unit. Our experience tends to suggest that infusion of FFP is not usually necessary.

The risks of withdrawing anticoagulation therapy for elective surgery are not inconsiderable. Several such patients have been admitted to our Regional Cardiothoracic Unit with life-threatening thromboembolic complications as a result of this practice, despite the use of prophylactic low dose heparin and/or antiplatelet drugs. Some of these complications have required emergency open heart surgery. We believe that the risks of increased haemorrhage from continuous warfarin therapy are considerably less than the risks of thromboembolic complications of temporarily withdrawing therapy. Furthermore, we do not think it necessary to change the method of anticoagulation from warfarin to heparin over the peri-operative period as suggested by Tscholl *et al.* (1980).

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The Treatment of Sphincter Strictures

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Summary—A group of 25 patients with strictures of the membranous urethra following transurethral resection of the prostate (TURP) were investigated and treated initially by careful urethral dilatation. This controlled the stricture in 14 patients, 6 of whom continued with occasional dilatation or self-catheterisation to maintain control; 8 required an artificial urinary sphincter (AUS) and 2 required a "clam" ileocystoplasty for detrusor instability. Eleven had persistent or recurrent strictures requiring urethroplasty. Nine underwent bulbo-prostatic anastomotic urethroplasty, 4 with simultaneous bladder neck reconstruction and 5 with subsequent implantation of an AUS; 2 had a preputial patch urethroplasty with subsequent implantation of an AUS. Four of the 9 patients with a urethroplasty and an AUS are satisfactory, 1 developed a recurrent stricture and 2 developed erosions. Two of those with a bulbo-prostatic anastomosis and bladder neck reconstruction are satisfactory and 2 are incontinent.

These results were compared with those of 18 other patients who underwent bladder neck reconstruction and 12 who had a urethroplasty in conjunction with an AUS for reasons other than a post-TURP sphincter stricture. The success rate of bladder neck reconstruction was 55% and the success rate of urethroplasty in conjunction with an AUS was 83%, but the main complication of AUS implantation, erosion, was a more serious problem than failure of bladder neck reconstruction. However, the much higher success rate makes AUS implantation a more satisfactory procedure. Surgery should be avoided if at all possible and reliance placed on urethral dilatation.

A sphincter stricture is defined as a stricture of the membranous urethra in which urethral disruption has not occurred and in which the loss of sphincter function is at least as important as the obstructive effect of the stricture itself.

The commonest causes of sphincter strictures are transurethral resection of the prostate and external trauma. Following external trauma that has not disrupted the urethra completely, the bladder neck is almost always competent and, in the absence of detrusor dysfunction, continence is therefore maintained; thus the stricture can be treated in isolation. On the other hand, following transurethral resection of the prostate there is also loss of bladder neck function resulting in incontinence and the stricture cannot be treated in isolation from the incontinence. The problem, therefore, is to preserve sphincter function and thereby continence, and to eliminate the obstruction caused by the stricture and prevent its secondary effects of poor bladder emptying and recurrent infection.

A review of the literature suggests that little attention, if any, has been paid to post-TURP sphincter strictures. This report describes our experience with a consecutive series of 25 patients.

Patients and Methods

The series comprised 25 men aged 51 to 74 years who were referred with obstructive sphincter strictures following TURP; 23 complained of incontinence and 2 had complete retention with indwelling suprapubic catheters. Of the 23 incontinent patients, 15 had a peak flow rate less than 5 ml/s and a stricture which was clearly shown on ascending urethrography and micturating cystography. Eight had a stricture which was shown on

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ascending urethrography but were uncatheterisable for a micturating cystogram and unable to void sufficiently to give a valid flow study.

The initial management of all of these patients was endoscopic evaluation and urethral dilatation. The ascending urethrogram and micturating cystogram were repeated 6 to 8 weeks later and a video-urodynamic study obtained. Repeat endoscopy and urethral dilatation were performed, according to the radiological findings, approximately 1 month later, *i.e.* 3 months after the initial endoscopic evaluation.

A further TURP was performed in those shown urodynamically to have outflow obstruction but radiologically to have no evidence of a stricture.

If further stricture recurrence was mild or infrequent, the patient was treated by either occasional dilatation or self-dilatation by self-catheterisation; if the stricture recurred frequently or severely, patients were advised to undergo urethroplasty, either by bulbo-prostatic anastomosis if the stricture was short, or by pedicled preputial patch urethroplasty (Mundy and Stephenson, 1988) if the stricture was more than 2 cm long or associated with a stricture-prone or strictured bulbar urethra. To regain continence the patient either underwent a simultaneous bladder neck reconstruction at the time of bulbo-prostatic anastomosis or the subsequent implantation of an artificial urinary sphincter.

Results

The endoscopic findings are shown in Table 1. Because of the sphincter stricture itself, it was not possible to be sure whether a patient had iatrogenic sphincter damage sustained by loop resection, but this was considered to be the case in 21 patients. In 4 patients it was considered that there was no iatrogenic sphincter damage caused by loop resection and the stricture and sphincter damge were thought to be due more to general intra-urethral trauma, spread of the diathermy current and possibly ischaemia.

Table 1 Endoscopic Findings

	No.
Sphincter stricture	25
Overt sphincter damage	21
Residual obstructive prostate	7
False passages	2
Stone/cavity/debris	9
Stricture-prone urethra	9
Other strictures	5

Table 2 Further Treatment

	No.
Stricture controlled (±)	14
Self-catheterisation	4
Occasional dilatation	2
AUS	8
"Clam" cystoplasty for D.I.	2
Recurrent stricture	11
BPA with subsequent AUS	5
BPA with BN reconstruction	4
Patch urethroplasty with AUS	2

Results		
Stricture controlled (±)	14	satisfactory outcome
Recurrent stricture	11	
BPA+AUS	1	recurrent stricture
	1	erosion
	3	satisfactory
BPA+BN recon.	2	wet
	2	satisfactory
Patch+AUS	1	erosion
	1	satisfactory

Video-urodynamic studies showed detrusor instability in 5 patients, with or without a poorly compliant bladder; 7 patients had residual prostatic obstruction in the absence of a radiologically demonstrable stricture (this being 6 weeks following dilatation).

The results of treatment are shown in Table 2. The stricture was controlled in 14 patients by the initial dilatation followed in 6 patients by either occasional dilatation or by occasional clean intermittent self-catheterisation. The other 8 patients subsequently underwent implantation of an AUS. Two patients underwent "clam" ileocystoplasty for control of detrusor instability; the other 3 patients with detrusor instability were controlled by Oxybutynin. All patients in this group were free of local problems such as false passages, cavities, stones or debris around the site of the stricture and had neither a stricture-prone urethra nor frank strictures elsewhere in the urethra.

Eleven patients had recurrent strictures requiring urethroplasty because they were not controlled by occasional dilatation. All of the patients with local complicating factors fell into this group. Of the 4 patients treated by simultaneous bladder neck reconstruction, 2 had a satisfactory result and 2 remained incontinent. Of the 7 patients who had a subsequent implantation of an AUS, 4 were satisfactory, 1 developed a recurrent stricture at the site of the bulbo-prostatic anastomosis and 2 developed a urethral erosion.

Because of the small numbers of patients in each of these groups, these latter results were compared with those in a group of 18 patients who underwent bladder neck reconstruction for problems other than post-TURP sphincter strictures and a further group of 12 patients undergoing urethroplasty and simultaneous or delayed implantation of an AUS for reasons other than a post-TURP sphincter stricture. In the former group, 10 of the 18 had a satisfactory result from bladder neck reconstruction (55%) and 8 (45%) remained incontinent. In the latter group, 10 of the 12 patients were continent after a urethroplasty and implantation of an artificial sphincter (83%) and 2 developed urethral erosions (17%).

Discussion

Strictures following TURP are not unusual. Indeed, it is common to observe "rifling" of the urethra with a grey urothelium in the penile and bulbar urethra even in the absence of an overt stricture. Treatment of such strictures by urethroplasty is not satisfactory because of a tendency for the stricture to recur at either end of the (patch) urethroplasty or elsewhere within the urethra. Strictures of the membranous urethra are particularly difficult because they compromise sphincter function in a patient who has had the bladder neck sphincter mechanism ablated by the prostatic resection. The aim of treatment is therefore more concerned with preservation of sphincter function than with elimination of the stricture. Indeed, in the absence of complicating factors such as chronic retention, obstructive nephropathy or recurrent urinary infection, the stricture is best ignored if the patient is not incontinent.

Treatment is necessary when a patient with a sphincter stricture is both obstructed and incontinent. The treatment least likely to cause further sphincter damage is careful urethral dilatation, which is less traumatic than urethrotomy or urethroplasty. The results of this study suggest that in the absence of local complicating factors at the site of the stricture or elsewhere in the urethra, dilatation is likely to control the stricture successfully and maintain reasonable continence in about half of the patients. In the remainder, an AUS is required. As with all forms of post-prostatectomy incontinence, detrusor instability, when present, is usually the most disabling lower urinary tract abnormality and will sometimes require cystoplasty in those unresponsive to or unable to tolerate Oxybutynin.

When there are local complicating factors or when the urethra is generally stricture-prone, occasional dilatation seems unlikely to be satisfactory, although it should be tried. Unfortunately, the results of a urethroplasty combined with either artificial sphincter implantation or bladder neck reconstruction are satisfactory in a little more than half of the patients so treated. These results are very disappointing. Our own experience of bladder neck reconstruction in other situations is not much better. The results of AUS implantation in conjunction with urethroplasty are much better, but when erosion occurs it is serious. The overall impression is that if surgery is required, an AUS will give the best results, but surgery is best avoided. Erosion in such patients is probably related firstly to the presence of a suture line close to the AUS cuff, secondly to a reduction in urethral blood supply as a result of the mobilisation required for bulbo-prostatic anastomosis, and thirdly to the (presumed) poor vascularity of the urethra as a whole (as a result of peripheral vascular disease) in many patients in the age group undergoing TURP; rifling of the urethra is probably another manifestation of the same process.

Although it is not generally considered advisable to implant an AUS cuff around the bladder neck after prostatic surgery because of fibrosis, the best treatment for those patients with sphincter strictures who cannot be controlled by gentle dilatation seems to be a bulbo-prostatic anastomotic urethroplasty, a reconstruction of the bladder neck, omental wrapping of the reconstruction and placement of an AUS cuff at this site where vascularity is probably better than in the urethra.

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Acquired Ventral Penile Curvature: Spongiofibrosis Caused by Urethral Manipulation

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Summary—Fibrosis of the corpus spongiosum, caused by urethral manipulation, and the resulting ventral penile curvatures are known as the urethral manipulation syndrome. This acquired, largely iatrogenic deformity is noticed only by sexually active patients.

Partial, gradual disappearance of glans engorgement and irregularities palpable along the penile urethra associated with ventral curvature are constant findings. The post-manipulative ventral curvature can be transient, disappearing when the inflammatory process subsides or the repeated urethral manipulation ceases. Since fibrosis of the corpus spongiosum begins with urethral inflammation, patients in whom irregularities of the penile urethra are observed during urethrography should be questioned about any erectile deformity.

Surgical treatment is indicated when the deformity interferes with sexual intercourse or is accompanied by severe urethral strictures.

Penile deviations are either congenital or acquired curvatures of the erect penis. Since Kelâmi (1984) described a new syndrome under the name 'urethral manipulation syndrome' (UMS), we have observed 3 patients in whom the ventral deviation developed after transurethral surgery.

UMS is an acquired, mostly iatrogenic penile deformity caused by fibrotic changes of the corpus spongiosum. In rare cases the patient himself causes an inflammatory reaction by inserting foreign bodies into his urethra for mental or masturbatory reasons. Male patients performing self-catheterisation may develop UMS. Inflammation of the corpus spongiosum develops as a result of traumatic catheterisation, reaction to urethral catheter material (Smith and Neligan, 1982; Blacklock, 1986; Talja *et al*., 1986), repeated urethral dilatation and cystoscopy or transurethral surgery. The fibrotic urethra, acting as a bowstring during erection, causes the bending of the penis. Since the fibrosis develops in the corpus spongiosum, the deviation is always ventral. UMS can be noticed only by a patient who is sexually active and when the fibrosis is at the penile urethra. Fibrosis of the more proximal urethra cannot cause penile bending for obvious reasons.

Patients and Methods

We present 3 cases of UMS observed during the last few years. All were referred to our 'Penile Deviation Clinic' by family practitioners or urologists. To arrive at an objective evaluation of the curvature a detailed case history was obtained. The deformity appeared a few months after transurethral or open prostatectomy in all patients and was accompanied by some degree of pain along the urethra during erection. When questioned specifically, patients reported gradual, partial or total disappearance of glans engorgement during erections. Palpation of the penis revealed cord-like nodular thickenings along the penile corpus spongiosum. Autophotography of the erect penis documented the ventral bending. Urethrography revealed corrugations at the penile urethral lining.

Case 1. A 62-year-old patient developed severe downward bending of the erect penis after TURP performed 8 months before referral. He also complained of weakened urinary stream which developed concomitantly. A cord-

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like nodular thickening at the peno-scrotal angle and fibrotic thickening along the penile urethra were palpated. Urethrography revealed irregularities caused by moderate strictures along the anterior urethra (Fig. 1). Since urethral dilatation and follow-up did not show any amelioration in the curvature an internal urethrotomy combined with Nesbit corporoplasty (Nesbit, 1965) was performed through an infrapubic incision.

Case 2. Following prostatectomy, a 63-year-old patient developed a severe urethral stricture accompanied by marked ventral curvature of the erect penis. The stricture was dilated several times. Since the curvature did not interfere with penetration and the patient decided that the urinary stream was adequate, he discontinued the dilatations. Five months later he was admitted with urinary retention caused by urethral occlusion which was dilated under anaesthesia to 8 F. The fibrotic 6-cm segment of the penile urethra was resected and the gap was reconstructed by a tubularised septum pedicled scrotal skin graft (Yachia, 1988). One year after surgery the penis was straight and the patient was able to pass urine freely.

Case 3. A 61-year-old patient developed urethral strictures after TURP. Urethrography showed fibrotic changes along the penile urethra and a stricture at the membranous part (Fig. 2). The distal urethra allowed passage to an 18 F catheter but the membranous stricture required treatment with internal urethrotomy. The patient reported a mild ventral curvature only after urethrography revealed urethral corrugations and he was questioned about his erections. He is undergoing periodic urethral dilatation and the curvature is followed up by autophotography every 3 months.

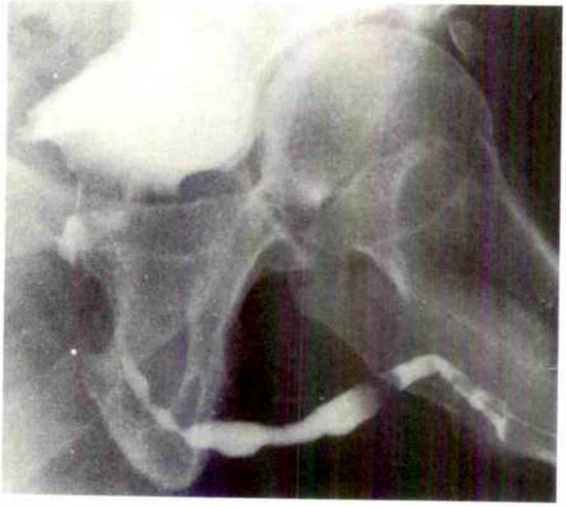

Fig. 1 Ascending urethrography of same patient showing corrugations of penile urethra and the more proximal strictures.

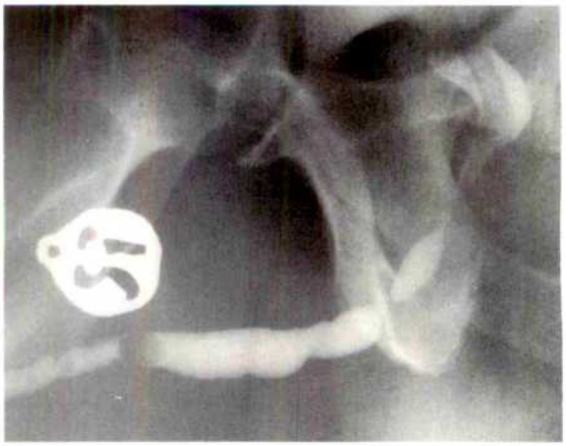

Fig. 2 Urethrography of Case 3 showing corrugations of penile urethra and the membranous stricture.

Discussion

To date, urethral inflammation of traumatic or infectious origin was considered one of the aetiological factors in the development of Peyronie's disease. Smith (1969) suggested that the initial pathology in this disease was urethritis causing an inflammatory reaction and fibrosis in the corpora. Later, various authors reported that approximately one-tenth of their patients with Peyronie's disease had a history of manipulative urethral trauma before the onset of symptoms and the ventral deformity (Byström and Rubio, 1976; Chilton, 1982; Pryor *et al.*, 1983). No involvement of the corpus spongiosum is described in Peyronie's disease, where the pathology is in the tunica albuginea of the corpora cavernosa and the intercavernosal septum; however, in UMS there is always inflammation and fibrosis of at least part of the penile corpus spongiosum and the aetiological factor is always urethral manipulation. UMS also differs from the urethral strictures which may develop after untreated or mal-treated purulent urethral infections such as complicated gonorrheal urethritis, which was often encountered before the antibiotic era.

When questioned about their erections, many patients who have undergone repeated urethral manipulation or transurethral surgery complain of pain along the urethra and some report that a ventral curvature developed gradually. In the vast majority, the pain disappears as the urethral inflammation subsides and the curvature straightens spontaneously after urethral instrumentation ceases (Kelâmi, 1984). Some patients continue to complain of penile deformity interfering with their sexual life.

The history of the disease and palpatory findings are generally sufficient for diagnosis. Partial or total disappearance of glans engorgement during erection is an important symptom which may show the degree of fibrosis in the corpus spongiosum. In some patients the changes are so severe that the ventral curvature can be observed even without an erection. Photography of the erect penis is an objective method of evaluating the degree of the curvature. This can either be done by the patient himself or by his partner in the privacy of their home (Kelâmi, 1983, 1985) or by the urologist after inducing an erection with an intracorporeal injection of papaverine (Desai and Gingell, 1987). Although Kelâmi (1984) stated that no structural changes are revealed by sonography, the depth of the spongiofibrosis in UMS can be seen in penile sonography (Hamm *et al.*, 1984; Gluck *et al.*, 1988; Merkle and Wagner, 1988). This technique is useful for documenting the spongofibrosis and for differentiating UMS from ventral penile deviation caused by Peyronie's disease. The fibrotic thickenings or calcified plaques of the tunica albuginea of the corpora cavernosa found in Peyronie's disease are not present in UMS. No pathology can be found in congenital penile curvatures by means of sonography. Because we encountered no difficulties in diagnosis, no sonographic evaluations were performed in our patients. However, we found urethrography, coupled with palpatory findings, to be most informative for diagnosis, especially in reticent patients. Since the urethral mucosa is always involved in the inflammatory process, irregularities along the penile urethra are invariably found during urethrography. These irregularities may appear with or without urethral strictures and this finding can be an early sign of the developing fibrosis. If penile urethral corrugations are observed during urethrography patients should be questioned about their erections. However, some patients are too embarrassed to discuss the matter and some do not know that these deformities can be treated.

Why only some patients develop spongiofibrosis is not clear. Not every chronic inflammation or trauma of the urethra causes fibrosis in the corpus spongiosum and this is a subject for further investigation.

Treatment of UMS should be individually designed for each patient. If the curvature does not interfere with the patient's sexual life, no surgical treatment is necessary. UMS curvatures can be straightened either by Nesbit corporoplasty or by implantation of a semi-rigid penile prosthesis if there is an accompanying erectile deficiency. Replacement urethroplasty may be indicated in curvatures accompanied by severe and almost impassable urethral strictures.

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Testicular Size in Infertile Men: Relationship to Semen Characteristics and Hormonal Blood Levels

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Summary—Testicular volume was assessed in 1029 infertile men and found to be normal in 704; 71 patients had unilateral and 213 had bilateral testicular hypotrophy; 4 had unilateral and 37 had bilateral atrophy. Sperm count and motility decreased in accordance with testicular volume. The lowest mean sperm counts and lowest mean motility percentages were found in patients with bilateral testicular atrophy. An increase in mean FSH and LH was also significantly linked to decreasing testicular volume; the increase in the former was not related to a drop in sperm count.

A significant correlation was found between testicular volume and spermatogenesis and testicular volume is considered to be a reliable indicator of testicular function.

It is now accepted that testicular volume is a realiable indicator of germinal cell density (Muller and Skakkebaek, 1983) and gonadal development in prepubescent and pubescent children as well as in adults (Rundle and Sylvester, 1962). Testicular size has been studied in men with normal (Rundle and Sylvester, 1962; Takihara *et al.*, 1983; Handelsman *et al.*, 1984; Pualivai, 1984) and pathological spermatogenesis (Farkas and Szollosi, 1986; Comhaire *et al.*, 1987) but it has not been established that testicular volume is useful in predicting sperm quality.

The aim of this retrospective study of 1029 infertile men was to investigate the relationship between testicular volume and spermogram characteristics, and also between testicular volume and hormonal parameters. The predictive value of testicular volume with regard to sperm quality was also evaluated.

Patients and Methods

Of 2469 infertile men seen at this Centre, 1029 were selected for this study. Clinical examination showed them to have no abnormal pathology of the vas deferens or epididymis and no cryptorchidism or clinical varicocele. Sperm analysis was performed in every case and hormone analysis in 402.

Scrotal examination and testicular size evaluation

All consultations were carried out by the same clinician (F.P.) and included medical history, the presence of associated pathology and the duration of infertility. The essential part of the consultation was the physical examination, routinely carried out with the patient standing, buttocks against the examination couch in order to ensure relaxation of the cremaster muscles. Any abnormality of the genital organs (epididymis, vas deferens, presence or absence of clinical varicocele, position of the testes) was investigated. Both 6-ml and 15-ml models of the Prader orchidometer (Prader, 1966) were used to assess testicular volume as follows. The testis was palpated with both hands and classified as (1) normal, if the volume was considered to be equal or greater than the 15-ml model, (2) atrophic, if the volume was less than the 6-ml model and (3) hypotrophic, if the volume lay between the above 2 groups (Takihara *et al.*, 1983; Handelsman *et al.*, 1984; Pualivai, 1984; Handelsman and Staraj, 1985; Farkas and Szollosi, 1986).

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Semen analysis

Sperm analysis was performed on semen recovered after 3 days' abstinence. Each sample was placed in an incubator at 37°C and examined within 1 h. The volume of semen was measured by direct reading on a graduated cylinder. Sperm counts were performed using a Mallassez cell (Rogo and Co., Arcueil, France) as follows. Following 20-fold dilution in a sodium bicarbonate-formol solution, an aliquot of the sperm sample was placed between the Mallassez cell and an overlying coverslip; this volume corresponded to 1 mm^3. Motility after 1 h was read under an optical microscope and expressed as a percentage of progressive motility (sperm crossing the visual field). The percentage of morphologically normal spermatozoa was determined after examination of 100 fixed and stained spermatozoa (David *et al.*, 1975). Since analysis of the latter parameter was not possible when the sperm count approached azoospermic levels, it could not be recorded for every patient. The total sperm count was obtained by multiplying semen volume by sperm count/ml.

Hormone analysis

Hormone analysis was performed using a radioimmunoassay method for FSH (IRE, Belgium; Standard MRC 69/104) and LH (Behring; Standard MRC 68/40), and using (^3H) testosterone (Bio-Merieux, France) plus steroid extraction for testosterone measurement. Normal laboratory control values (n = 50) were: FSH 2.7–9.1 mIU/ml; LH 2.8–10.8 mui/ml; testosterone 4.0–6.0 ng/ml. The coefficient of inter- and intra-variability was less than 10%. Statistical analysis was performed using Student's *t* test and the chi-squared test.

Results

Of the 1029 men studied, 704 had normal testicular size and 325 had the following abnormal measurements: unilateral hypotrophy (71), bilateral hypotrophy (213), unilateral atrophy (4), bilateral atrophy (37). The 4 patients with unilateral atrophy have been omitted from the Tables. One patient in this group was azoospermic (FSH 24 mIU/ml), 2 were oligozoospermic (FSH 7 and 6.3 mIU/ml) and the fourth was normospermic (FSH not measured).

Table 1 shows a significant correlation between reduction in testicular size and previous history of genitourinary problems. Only 22.5% of men in the normal group had a medical history compared with 35 to 53% in the other groups.

Table 2 shows the nature of the genitourinary history with respect to testicular size. Although a history of infection occurred most frequently in men with normal testicular dimensions (53%), a history of ectopy or cryptorchidism was most frequent in men with reduced testicular size (42–54%).

Table 3 shows the mean volume of ejaculate, sperm count, total sperm count, percentage of motile spermatozoa and morphologically normal spermatozoa with respect to the various categories of testicular size for men without azoospermia. The percentage of azoospermia was 10, 21, 50 and 86.5% respectively in patients with normal testicular size, unilateral hypotrophy, bilateral hypotrophy and bilateral atrophy.

The volume of ejaculate did not vary with testicular size. Sperm count and total sperm count differed significantly between patients with normal testicular size and those with reduced size. The lowest mean sperm count and mean total sperm counts were found in the bilateral atrophy group (mean ± SD $0.6 \pm 1 \times 10^6$/ml and $1.8 \pm 2.9 \times 10^6$/ejaculate).

A significant reduction in motility was found between the patients with normal testicular size and those with bilateral hypotrophy. The lowest motility was observed in patients with bilateral atrophy (mean ± SD 11% ± 10%) but this difference cannot be considered significant in view of the small number of patients. The percentage of normal sperm did not vary in relation to testicular size.

Table 4 shows the mean sperm count and mean

Table 1 Patients with and without Previous History of Genitourinary Problems in Relation to Testicular Size

Testicular	*Without genitourinary history*	*With genitourinary history*
Normal	545	159
Unilateral hypotrophy	33	38
Bilateral hypotrophy	129	84
Bilateral atrophy	24	13

X^2: $P < 0.001$.

plasma FSH, LH and testosterone with respect to testicular size in the non-azoospermic men who underwent hormone analysis. There was no statistically significant difference in sperm counts between the total population of non-azoospermic men (Table 3) and the population that underwent hormone analysis (Table 4). The mean FSH concentration differed significantly between the group with normal testicular size and the groups with diminished testicular size. Furthermore, mean FSH concentration increased with the degree of testicular reduction. The mean concentration of LH differed between the normal group and the group with bilateral hypotrophy. The mean concentration of testosterone did not differ significantly.

Table 2 Previous History in Relation to Testicular Size

	History		
	Infectious (%)	*Cryptorchidism or ectopy (%)*	*Other* (%)*
Normal dimensions	53	18	29
Unilateral hypotrophy	37	42	21
Bilateral hypotrophy	39	49	12
Bilateral atrophy	46	54	0

* Surgical treatment for inguinal hernia, exploration of testes and epididymis.

Table 5 shows the variations in mean FSH in a given sperm count group with respect to testicular volume. In azoospermic and oligozoospermic patients, mean FSH concentration increased with reduction in testicular volume.

Table 6 shows the percentage of men with azoospermia, oligozoospermia and normospermia in the 4 groups.

Table 3 Sperm Characteristics of Non-azoospermic Infertile Men in Relation to Testicular Size

Testicular size		*Volume*	*Sperm count (× 10^6/ml)*	*Total sperm count (10^6/ejaculate)*	*Percentage of motility*	*Percentage of normal spermatozoa*
Normal	n	631	631	631	631	473
	mean	3 3	51 5	148.7	41	33.5
	(SD)	(1.7)	* (65.0)	* (180.5)	(22.5)	(16.6)
Unilateral hypotrophy	n	56	56	56	56	36
	mean	3.1	* 18.0	* 49.9	† 36	38.6
	(SD)	(1.4)	(20.0)	(59.1)	(21)	(16.7)
Bilateral hypotrophy	n	107	‡ 107	‡ 107	107	47
	mean	3.2	7.5	25.4	33	34.9
	(SD)	(1.3)	(22.5)	(76.4)	(23)	(16.2)
Bilateral atrophy	n	5	5	5	5	1
	mean	3.2	0.6	1 8	11	40
	(SD)	(2.1)	(1 0)	(2.9)	(10)	(0)

n = number of patients. SD = standard deviation
* = $P < 0.001$. † = $P < 0\ 01$ ‡ = $P < 0\ 05$

Table 4 Hormone Analysis and Sperm Count in Non-azoospermic Infertile Men in Relation to Testicular Size

Testicular size		*Sperm count (10^6/ml)*	*FSH (mIU/ml)*	*LH (mIU/ml)*	*Testosterone (ng/ml)*
Normal (n = 174)	Mean	27.1	6.2	6.3	4.6
	(SD)	(35.2)	† (5 2)	(5.3)	(2.4)
Unilateral hypotrophy (n = 29)	Mean	18.3	* 9.6	‡ 8.4	4.7
	(SD)	* (18.3)	‡ (5.9)	(4.4)	(1.8)
Bilateral hypotrophy (n = 60)	Mean	† 6.9	13.9	9.1	4 4
	(SD)	(26.2)	(10 6)	(7.5)	(1.7)
Bilateral atrophy (n = 5)	Mean	0.8	19 5	6.7	4 6
	(SD)	(1.0)	(14.5)	(3.3)	(2.1)

n = number of patients. SD = standard deviation
* = $P < 0.001$ † = $P < 0.01$. ‡ = $P < 0\ 05$

Table 5 Mean Values of FSH (mIU/ml) in Relation to Testicular Size and Sperm Count

Testicular size		*Azoospermic men*	*Oligozoospermic men Sperm count < 20.10^6/ml*	*Normospermic men Sperm count ≥ 20.10^6/ml*
Normal	n	41	105	69
	mean	10.4	6.1	6.3
	(SD)	(10.2)	(5.2)	(5.2)
Unilateral hypotrophy	n	5	16	13
	mean	14.9	10.1	8.8
	(SD)	(10.7)	(7.0)	(4.4)
Bilateral hypotrophy	n	65	58	2
	mean	19.3	14.2	6.1
	(SD)	(10.9)	(10.7)	(3.0)
Bilateral atrophy	n	20	5	—
	mean	29.4	19.5	
	(SD)	(15.4)	(14.4)	

n = number of patients SD = standard deviation
* = $P<0.001$. † = $P<0.01$.

Table 6 Percentage of Men with Azoospermia, Oligozoospermia and Normospermia in Relation to Testicular Size

	Normal testicular size	*Unilateral hypotrophy*	*Bilateral hypotrophy*	*Bilateral aplasia*
Azoospermia	10	21	50	86.5
Oligozoospermia	35	52	47.5	13.3
Normospermia	55	27	2.5	0

Discussion

Determination of testicular volume was performed by the same clinician (F.P.), thus avoiding variations of the kind reported by Takihara (1983). Although not performed by indirect measurement (Lamber, 1951; Hansen and Torben, 1952; Rundle and Sylvester, 1962), the use of 2 models of the Prader orchidometer (6 and 15 ml) enabled patients to be divided into 4 groups: those with normal testes, those with unilateral testicular hypotrophy, those with bilateral hypotrophy and those with bilateral atrophy. The fifth group (unilateral atrophy) was insufficiently represented to be included in the study (see Results).

The results of this study revealed that reduction in testicular volume was linked to the individual's genitourinary history and was found most often when the testis was either hypotrophic or atrophic. The preponderance of testicular cryptorchidism or ectopy in the event of abnormal testicular size is a further argument in favour of early treatment of these conditions (Hadziselimovic *et al.*, 1975).

Testicular volume is considered to be an indicator of spermatogenesis. Some authors consider that at least 90% of testicular volume consists of seminiferous tubules (Kothari and Gupta, 1974; Sherins and Howards, 1978). A correlation has been shown between testicular volume and germinal cell content and diameter of the tubules (Muller and Skakkebaek, 1983). Prader (1966) has suggested that normal spermatogenesis is possible only with testes of normal size. A progressive reduction in sperm count and total sperm count has been reported in infertile men by Comhaire *et al.* (1987) with an associated decrease in total testicular volume. The results of this study support these arguments. Firstly, the number of azoospermic patients increases with the degree of reduction in testicular volume. Secondly, when azoospermia is excluded, sperm count and total sperm count decrease as testicular volume decreases. The presence or absence of a genitourinary history does not affect the sperm count irrespective of testicular size and therefore this drop in sperm count can be attributed to a reduction in testicular volume. Finally, the percentage of mobile spermatozoa found in the ejaculate decreases with testicular size.

The volume of ejaculate does not vary in relation to testicular size. This is explained by the fact that 80 to 90% of the semen volume is composed of secretions from secondary glands (Eliasson, 1981).

A diminution in the percentage of morphologically normal spermatozoa linked to the reduction in testicular volume has been found in fertile men (Aribart *et al.*, 1986). The infertile men in the present study showed no variation in the percentage of morphologically normal spermatozoa when testicular volume was reduced. However, these results require further investigation in view of the methodological bias: it was technically impossible to observe the morphological characteristics of sperm in patients with severe oligozoospermia (see Patients and Methods).

Together with a fall in sperm production, an increase in plasma FSH was found to be linked to the reduction in testicular volume. The increase observed in FSH concentration and the alteration in spermatogenesis are in agreement with the findings of other authors (Franchimont *et al.*, 1972; Stopelli and Dessole, 1982; Mikuz *et al.*, 1985). In the group with bilateral hypotrophy, an increase in LH was also found. The latter observation, together with stability in testosterone concentration, indicates a compensated Leydig cell dysfunction (Glass and Vigerski, 1980; Vermeulen, 1986). The finding of a mean testosterone concentration, stable with respect to testicular volume, was also reported by Aribart (1986).

The increase in FSH in those groups with a reduction in testicular volume is in agreement with the negative correlation between FSH and testicular volume reported by Franchimont *et al.* (1972), Handelsman *et al.* (1984) and Comhaire *et al.* (1987). This study also shows that an increase in FSH and a reduction in testicular volume are partially independent of the output of spermatozoa, since within the same sperm count group (azoospermic, oligozoospermic) we find an increase in FSH linked to the degree of reduction in testicular volume (Table 5).

Finally, we have shown that examination of testicular size has a certain predictive value regarding sperm count (Table 6). Thus a man presenting with infertility but showing no abnormality on clinical investigation has a 10% chance of being azoospermic. If he is not azoospermic, there is a 60% chance that the sperm count will exceed 20×10^6/ml. A man with unilateral hypotrophy has a 20% chance of being azoospermic and, if he is not, there is a 30% chance of the sperm count exceeding 20×10^6/ml. A man with bilateral hypotrophy has a 50% chance of being azoospermic and, if he is not, there is a less than 10% probability of his sperm count exceeding 20×10^6/ml. If a patient is found to have bilateral atrophy during clinical examination, the prognosis is considerably worse. He has a 90% chance of being azoospermic and, if he is not, the likelihood of his having a sperm count greater than 20×10^6/ml is negligible.

The existence of a relationship between testicular size and sperm count, and the predictive nature of testicular size concerning the presence of spermatozoa in the ejaculate, are arguments in favour of measuring testicular volume during the investigation of infertile patients. As suggested by Virji and Eliasson (1985), quantitative measurement of the testes could allow analysis of the production of spermatozoa as related to the volume of the testes. Such a study is currently being pursued in this centre.

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PAEDIATRIC UROLOGY

Ultrasound and Plain X-ray Screening in Childhood Urinary Tract Infection

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Summary—A group of 309 children over the age of 2 years was investigated with ultrasound and plain X-ray for suspected urinary infection. In 29 cases there were abnormal findings and in 10 the abnormalities were confirmed with cystography and intravenous urography. Of 280 children whose ultrasound and plain X-ray findings were normal, 26 re-presented with further symptoms and investigation with cystography and urography showed abnormalities in only 4. The remaining 254 children have remained well and have been spared the uncomfortable and potentially dangerous examinations of cystography and urography.

Increasing numbers of children are being referred with symptoms suggestive of urinary tract infection (UTI), often unproven bacteriologically, and there is a great need for simple methods of investigation. The time-honoured complete investigations of micturating cystography (MCU) and intravenous urography (IVU) are both unpleasant and, to some extent, dangerous; infections can be introduced with a cystogram and intravenous urography is not without its morbidity and mortality. They both have hazards of irradiation and, in these days of audit and pricing of all investigations, ultrasound has many advantages over the conventional studies of MCU and IVU. Thus the need for newer methods of screening children with UTI is obvious.

This study was designed to see if ultrasound (U/S) and a single plain X-ray of the abdomen including the kidneys, ureters and bladder (KUB) would be an effective initial screening procedure in the investigation of a selected group of children over the age of 2 years. Implicit in the study were 2 principles. First, if any anomaly was seen on the U/S and KUB, further conventional studies would be performed. Second, any child with severe illness associated with a UTI, such as fevers or loin pain, would usually be studied initially with MCU and IVU.

Patients and Methods

Between 1981 and 1988 635 children were investigated for suspected UTI; 303 were investigated initially with MCU and IVU and are not discussed further in this report; 332 children had U/S and KUB as the initial investigation, of whom 309 had adequate follow-up for the purposes of this report. The mean age of these 309 children was 6 years (range 2–16) and 56% were girls. Presenting symptoms are shown in Table 1; 80% of children had 2 or more of these symptoms; 39% had firm evidence of UTI (10^5 bacteria and >50 pus cells/

Table 1 Presenting Symptoms

Symptoms	%	*Symptoms*	%
Dysuria	26	Urgency	3
Frequency	20	Vaginal soreness	2
Abdominal pain	9	Difficult voiding	2
Enuresis	7	Balanitis	2
Daytime wetting	7	Vomiting	<2
Fevers	6	Convulsions	
Loin pain	6	Nocturia	
Haematuria	6	Offensive urine	

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cubic ml); 16% had an equivocal MSU result and 25% had no definite evidence of UTI. An MSU had not been done during the acute illness or the result was unknown in 20%.

Irrespective of symptoms, previous episodes or firm evidence of infection, all of these children had U/S and KUB. If these were both normal the child was discharged from the clinic with an explanation to the parents and the family doctor that most serious anomalies had been excluded but that reflux might have been missed. They were asked to report back for further investigations via the family doctor if symptoms recurred.

If any anomaly was found on screening with U/S and KUB, further appropriate investigations were performed, usually MCU and IVU.

The parents of all 309 children were contacted by telephone or letter between 1 and 8 years later (mean 3 years 3 months) to enquire about further symptoms and proven or suspected UTI.

Results

The results are shown diagrammatically in the Figure; 29 anomalies were suspected on U/S and KUB of which 10 (true positives) were shown to be clinically relevant (Table 2). Amongst the 19 false positives, in which an abnormality was suspected but not proved by further investigation, there was mild dilatation or other features that led us to suspect reflux, hydronephrosis, an ectopic ureter, a thick walled bladder and renal scarring.

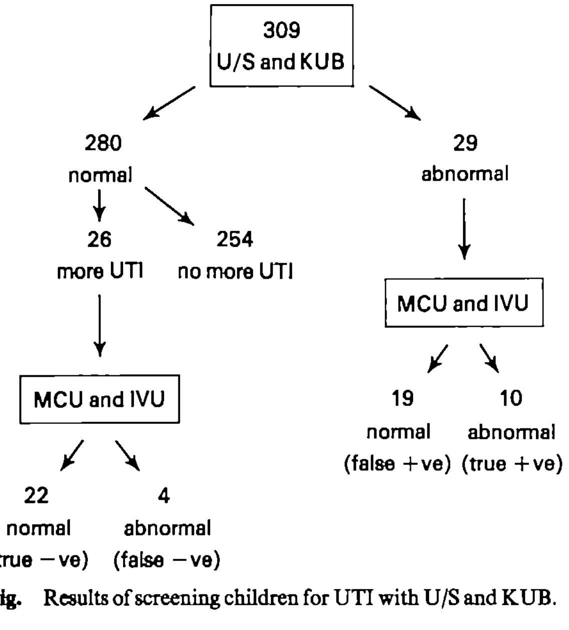

Fig. Results of screening children for UTI with U/S and KUB.

Table 2 Findings

	No.
False negatives	
Reflux (unilat. grade 3)	2
Renal stone	1
Renal scar	1
Total	4
True positives	
Hydronephrosis	3
Renal ectopia or duplex	3
Absent kidney	1
Megaureter	1
Thick bladder	1
Urethral valve	1
Total	10

In 280 children U/S and KUB were thought to be normal but 26 of these children re-presented after a mean interval of 1.3 years with further symptoms suggestive of UTI. The UTI was proved in 20 of these 26. MCU and IVU confirmed the normality of the child's urinary tract in 22 of the 26 and revealed an abnormality in only 4. These 4 false negatives are shown in Table 2; in 3 of these children there was a true UTI. Of the 22 children who were true negatives, 17 had a genuine UTI.

The sensitivity of U/S and KUB was 71% (10/14), whilst the specificity was 94% (276/295).

Of all of the symptoms, only abdominal pain was more common in the group of patients with a definite abnormality (35%) than in the group with normal findings (16%), but this difference was not significant ($P = >0.1$); 68% of infected urines showed coliform, 8% *Proteus* and 4% *Klebsiella*. It is interesting to note that only 2 of 18 patients with a *Proteus* infection had abnormal urinary tracts.

Discussion

Previous studies comparing U/S and KUB with intravenous urography in children with urinary infections have shown that major drainage anomalies are detected but reflux and scarring of the kidneys can be missed (Sherwood and Whitaker, 1984; Lindsell and Moncrieff, 1986). In this study we investigated an older group of selected patients to assess the efficacy of U/S and KUB alone as a screening procedure. Fourteen abnormalities were found in 309 children; 10 of these were detected on the initial U/S and KUB and 4 by MCU and IVU after the child had re-presented with further symptoms. Two questions must be answered. First, did the 4 children in whom the diagnosis was delayed suffer unnecessarily or come to any harm before the correct diagnosis was established? We believe not. Second, was it an advantage to 254 of 309 children (91%) to avoid an unnecessary MCU and IVU? We think so.

The reason why the incidence of abnormalities in this series is only 4.5% when the usual rate is approximately 40% (Smellie, 1980) is because many children with severe symptoms associated with proven UTI, and in whom there was a high index of suspicion of an underlying abnormality, were initially investigated with MCU and IVU. An alternative explanation is that we failed to detect anomalies on U/S and KUB amongst the 254 children in whom these were the only investigations. Although our subsequent contact with the parents by letter or telephone suggests that these children have remained infection-free, we continue to follow them up and accept that MCU and IVU might yet show an anomaly.

Reflux is prominent amongst the false negatives and this is hardly surprising since intermittent dilatation associated with reflux is easily missed by an ultrasound examination. The inability of U/S and KUB to detect reflux is perhaps emphasised by the fact that none was seen amongst the 10 true positives whilst there were 2 cases in the false negative group. The general practitioners and parents of children whose urinary tract appeared normal on screening with U/S and KUB were told that reflux may not have been excluded and therefore further UTI should be treated promptly with antibiotics. Over the age of 2 years, particularly if there have been previous UTIs, it is most unlikely that new or further scarring will occur (Hodson, 1981; Birmingham Reflux Study Group, 1987), suggesting that the natural history of the disease in this age group will not be altered by this "wait-and-see" policy.

We believe that the advantage of avoiding MCU and IVU in 254 selected children over the age of 2 years as the initial investigation for suspected UTI outweighs the disadvantage of missing reflux in 2 patients, a small stone in one and renal scarring in another. Although our concern must be that we may have missed other problems in this group of 254 children, a careful follow-up has, so far, not given us any reason to believe this.

The advantages of avoiding the costly, unpleasant and potentially dangerous investigations of MCU and IVU are obvious.

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Anterior Pelvic Osteotomy. A New Operative Technique Facilitating Primary Bladder Exstrophy Closure

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Summary—Posterior iliac osteotomy is a recognised method employed to facilitate and support anterior abdominal wall closure in patients with bladder exstrophy, but it adds considerably to the already lengthy procedure of bladder exstrophy surgery. Anterior pelvic osteotomy of the superior ramus of the pubic bone was developed to overcome this problem and to achieve a stable anterior pelvic ring with tension-free soft tissue closure. It can easily be performed after completing the bladder closure, without the need to turn the patient.

In bladder exstrophy surgery the closure of the bladder and bladder neck is followed by repositioning the bladder within the abdominal cavity. The key to success is to have a tension-free approximation of the previously widely separated pubic bones and of the anterior abdominal wall. The firm anterior pelvic ring normally prevents dehiscence, infection and prolapse of the reconstructed bladder. It will also allow for the suspension of the neourethra when it is constructed later. If surgery is performed within the first 2 weeks of life, the soft elastic pelvis often allows easy approximation without the need for pelvic osteotomy (Ansell, 1979; Lowe and Jeffs, 1983). If surgery is carried out later, and easy approximation is not feasible, then bilateral posterior pelvic osteotomy should be carried out (Jeffs *et al.*, 1982; Rickham and Stauffer, 1984). This is, however, an extensive procedure, necessitating turning the patient during surgery, needing 2 extra incisions and adding considerably to the operating time. In addition, it is not always free of complications and is not universally successful. An alternative technique was sought which would fulfil all of the criteria mentioned above, and anterior pelvic osteotomy seems to do so.

Patients and Methods

The edges of the ectopic bladder are first freed and then closed and the bladder neck and proximal urethra are reconstructed (Jeffs, 1978). The abdominal skin and subcutaneous tissues are then widely mobilised.

The insertion of the rectus muscle into the pubic bones is located (Fig. 1A) and the lateral border of the sheath opened. The postero-superior aspect of the pubic bone is approached through this window (Fig. 1B). The insertions of gracilis, the long and short adductor muscles are all located and identified.

The superior ramus is then demonstrated between these and the pectineus muscle by partially freeing the latter from its insertion. A spatula is inserted into the obturator foramen to displace laterally and so protect the obturator nerve. Complete osteotomy of the superior ramus is performed using a stout pair of scissors. It is advisable to make the osteotomy medial to the insertion of the inguinal ligament (Fig. 1C). If this is difficult or impossible to achieve, the inguinal ligament can be divided and reinserted laterally. The other side is then divided in the same way.

The medial aspects of both superior rami are tilted towards the midline and approximated (Fig. 1C). In this way a gap of 3 to 4 cm can easily be bridged, as the cartilaginous ischio-pubic junction acts as an articulation. The rectus sheaths are sutured together using interrupted polyglyconate sutures. If the gap between the divided ends of the pubic bone remains too wide for spontaneous

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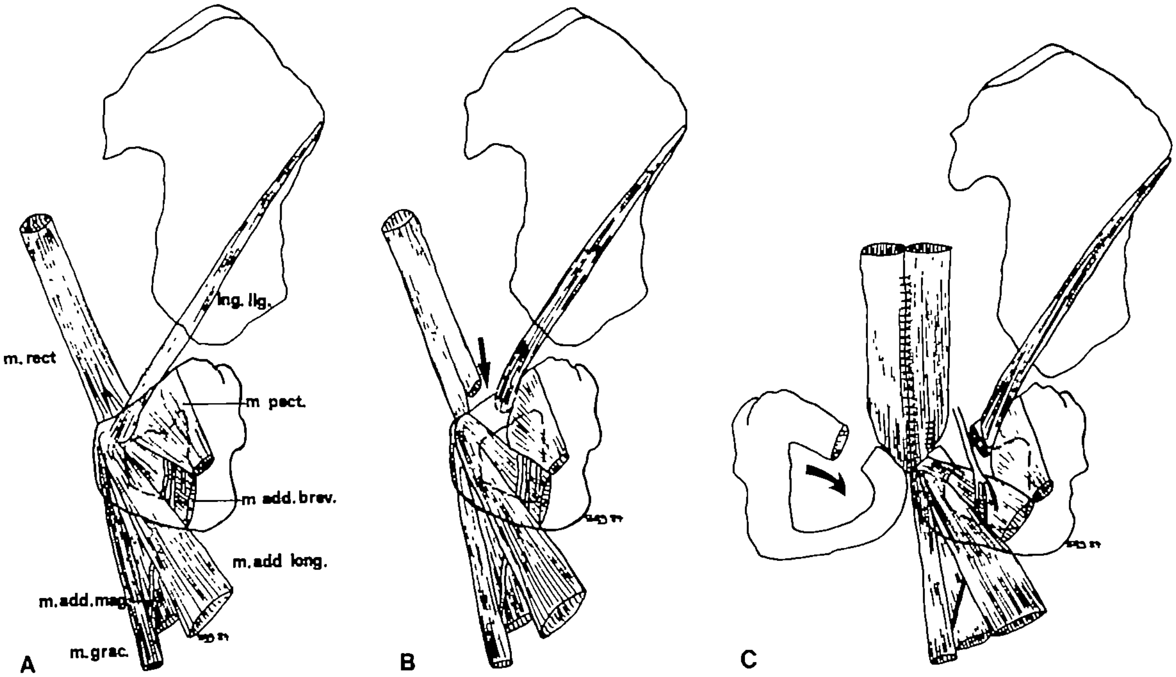

Fig. 1 Schematic demonstration of anterior osteotomy of the superior ramus of the pubic bones (A) Anatomy of muscles which have to be identified prior to osteotomy (B) Site of osteotomy (arrow) between adductor muscles and pectineus. (C) State after performing bilateral osteotomy Arrow indicates tilting movement towards the midline

reossification to occur, a free easily harvested rib transplant can be interposed.

Suturing of the symphysis should be avoided if possible (Mollard, 1980); if not, a few polyglyconate sutures can be inserted. The generously mobilised skin-submucosal flaps are then approximated without tension using fine nylon sutures.

Results

Experimental work was carried out on 6 neonatal cadavers. This technique has been successfully performed in neonates in a small series of 4 patients (Frey and Cohen, 1988). Two patients were female and 2 male. Following the anterior osteotomy described, complete adaptation of the symphysis was achieved and a tension-free closure of the abdominal wall was possible in all 4 cases.

Two patients had complete and uneventful primary healing. One developed a small skin dehiscence with partial bladder prolapse, possibly due to an excessively wide bladder neck following its reconstruction. The fourth patient developed a severe, deep wound infection, resulting in complete breakdown of the repair. In no case has osteomyelitis of the osteotomised pubic bones developed.

Discussion

It is too early to comment on the long-term results of this new operation, but the criteria for successful bladder reconstruction are already fulfilled. The abdominal wall can be closed without undue tension and this should help to prevent wound dehiscence. The anterior bony pelvic ring and consequently the pelvic floor are closed. A protective and stable cover for the reconstructed bladder, bladder neck and proximal urethra has been achieved. When the neo-urethra is constructed later, its suspension under an intact symphysis is feasible.

In the male, approximation of the corpora cavernosa should be facilitated because the pubic bones have been brought together and this should help in future penile surgery of the remaining epispadias.

It is not known how quickly, if at all, the defects in the divided pubic bones will spontaneously correct themselves. The question of what length of bony defect would benefit by a bridging rib transplant also remains unanswered. The risk of a compromised gait cannot be predicted, but this would have to be compared with the abnormal gait that already occurs in some cases of closed bladder exstrophy.

Anterior pelvic osteotomy, performed at the same time as primary bladder and abdominal wall closure, is a simple and effective procedure. The operating time is often shorter than when posterior pelvic osteotomy is added to primary closure. The procedure substantially improves the immediate outcome of bladder exstrophy closure.

Despite the problems which occurred during the learning curve of this new technique, we recommend it for the difficult problem of closure of bladder exstrophy.

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Inter-observer Variation in Assessment of Undescended Testis

Analysis of Kappa Statistics as a Coefficient of Reliability

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Summary—In a prospective study the inter-observer variation in the diagnosis of undescended testis was analysed. Two physicians assessed independently the position and motility of the testes of 37 boys referred for undescended testis. The boys were examined in the supine and squatting positions. The observed agreement rate between the observers was 0.90 to 0.97. Using kappa (κ) statistics, the values were adjusted for the expected chance agreement; κ values between 0.47 and 0.81 were obtained, slightly higher values for patients in the supine position. Complete agreement on all observations was reached in 13.5% of the patients. Inter-observer variation may be a substantial source of bias in diagnosing the undescended testis and one of the reasons for the varying results in studies of hormonal treatment of this condition. It is also a fact that the number of orchiopexies in some countries exceeds the incidence of this condition.

The term undescended testis is defined as any disorder of testicular descent: retractile testes, ectopic testes, true retention (both bilateral and unilateral) and even intra-abdominal testes are covered by the term.

Classification within the groups has been widely discussed. Diagnosis, indications for and results of treatment are assessed by clinical examination of the groin and scrotum.

In recent years numerous studies on the effect of LHRH treatment have been carried out with reported success rates of 9 to 78% (Zabransky, 1981; de Muinck Keizer-Schrama *et al.*, 1986). In addition to variations in the definition of undescended testis and in the design of studies, another source of bias could be inter-observer variation. The aim of the present prospective study was to assess inter-observer variation in the diagnosis of undescended testis, defining only the position and motility of the testis.

Patients and Methods

The series comprised 37 boys (median age 6.0 years, range 2–11) referred consecutively for undescended testis to our out-patient clinic. The boys were examined independently by the same 2 observers, one a consultant in urology and surgery and the other a senior registrar with several years' surgical experience. The examinations were carried out in identical circumstances, within an interval of a few minutes, within the same room and with the same information available to each observer. The position and motility of the testes were examined with the patient in the supine and squatting positions and conclusions recorded immediately. Since no 'diagnosis' was made, the possibility of different diagnostic definitions within the term "undescended testis" was avoided. Some of the patients were included in a randomised clinical trial (unpublished) of intra-nasal LHRH treatment of undescended testis.

Statistical analysis and calculations

Inter-observer variation was analysed by kappa statistics. Kappa (κ) is a coefficient of pairwise agreement between observers first described by Cohen (1960). It adjusts the observed proportion of agreement between 2 observers (p_o) with the

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proportion of agreement expected solely by chance (p_e). Although kappa was originally proposed for measurement on nominal scales, Cohen (1968) suggested the weighted kappa (κ_w) as a coefficient of ordinal-scaled degrees of agreement (or disagreement). The overall value of kappa may be defined as a weighted average of the individual kappa values. The position and motility of the testes were registered on a K-point ordinal scale where $K=4$; the positions were registered as: non-palpable (I), inguinal (II), high scrotal (III), complete descent (IV). Motility was examined by caudal traction on the testes: non-mobile (i), hardly mobile (ii), to be manipulated to scrotal entrance (iii) or to be manipulated to the bottom of scrotum (iv). The patients received a score from both observers X and Y; the maximum difference between the scores was $K-1$, *i.e.* $[x-y] \leqslant K-1$.

The relative significance of each possible disagreement is quantified by the 'degrees of agreement' or 'weights' (Fleiss, 1981), which are between 1 and zero. In the present study this means that 'degree of agreement' in positions, for example, declines with an increasing difference between the recorded positions of the testes.

In contrast to other workers (Gjørup and Jensen, 1986), we defined the weights as

$$w_{xy} = 1 - \frac{(x-y)^2}{(K-1)^2} \qquad (1)$$

as proposed by Fleiss and Cohen (1973). In this case, kappa is conceptually identical with the intraclass correlation coefficient and also computationally identical, apart from a small term involving the factor 1/n (Fleiss, 1981).

The observed weighted proportion of agreement is then

$$p_{o(w)} = \sum_{x=1}^{K} \sum_{y=1}^{K} w_{xy}\, p_{xy} \qquad (2)$$

and the chance expected weighted proportion of agreement is

$$p_{e(w)} = \sum_{x=1}^{K} \sum_{y=1}^{K} w_{xy}\, p_{x\cdot}\, p_{\cdot y} \qquad (3)$$

Weighted kappa is given by

$$\chi_w = \frac{p_{o(w)} - p_{e(w)}}{1 - p_{e(w)}} \qquad (4)$$

Kappa can assume values between +1 and a negative worst possible value ($\geqslant -1$). In the case of perfect agreement κ is 1; $\kappa = 0$ when the observed agreement p_o is equal to the expected chance agreement p_e. Values above 0 indicate agreement greater than chance agreement; values below 0 indicate agreement less than chance agreement (Cohen, 1960). The appropriate standard error of κ ($SE_{(\kappa w)}$) is described elsewhere (Fleiss, 1981). The approximative confidence limits of kappa are given by $\kappa \pm 1.96$ SE, the interval including the true kappa value with a probability of 95% (Gjørup and Jensen, 1986). For testing the hypothesis that the underlying value of kappa is 0, the value of the critical ratio (z)

$$z = \frac{\kappa_w}{SE_{(\kappa w)}} \qquad (5)$$

may be referred to tables of the standard normal distribution (Fleiss, 1981).

Results

The relation between the observations of the 2 observers X and Y is shown in Figures 1 and 2. The mean differences and their standard deviations are noted in the legends to the figures. The disagreement between the 2 observers was equally distributed; neither showed a tendency to record a lower/higher position or a lower/higher motility (Wilcoxon's test: $P > 0.05$ for all pairs).

κ values, their 95% confidence limits, the standard error of κ, the observed agreement rate, the expected chance agreement rate, the critical ratio z and the corresponding *P* values for each set of observations are shown in the Table; κ varies significantly from O for all pairs of observations, which means the rate of the observed agreement was significantly higher than the rate of agreement achieved by chance alone. Complete agreement on all observations was achieved in 5 patients (13.5%; 95% confidence limits: 4.5–28.8%). κ values and the observed agreement rate were highest for patients in the supine position.

Discussion

The indications for treatment of the undescended testis are based on the results of physical examination of the inguino-scrotal region. In addition, the success of medical treatment is judged by this examination alone. This study analyses the precision of the diagnosis but not the accuracy of the findings, *i.e.* we studied the observers' agreement with each other and not with a 'true' answer (gold standard). The 2 observers knew that their clinical findings would be analysed, so they might have been more careful than usual in these examinations. Thus the "true" inter-observer variation may be even greater. Experience was not a factor in this

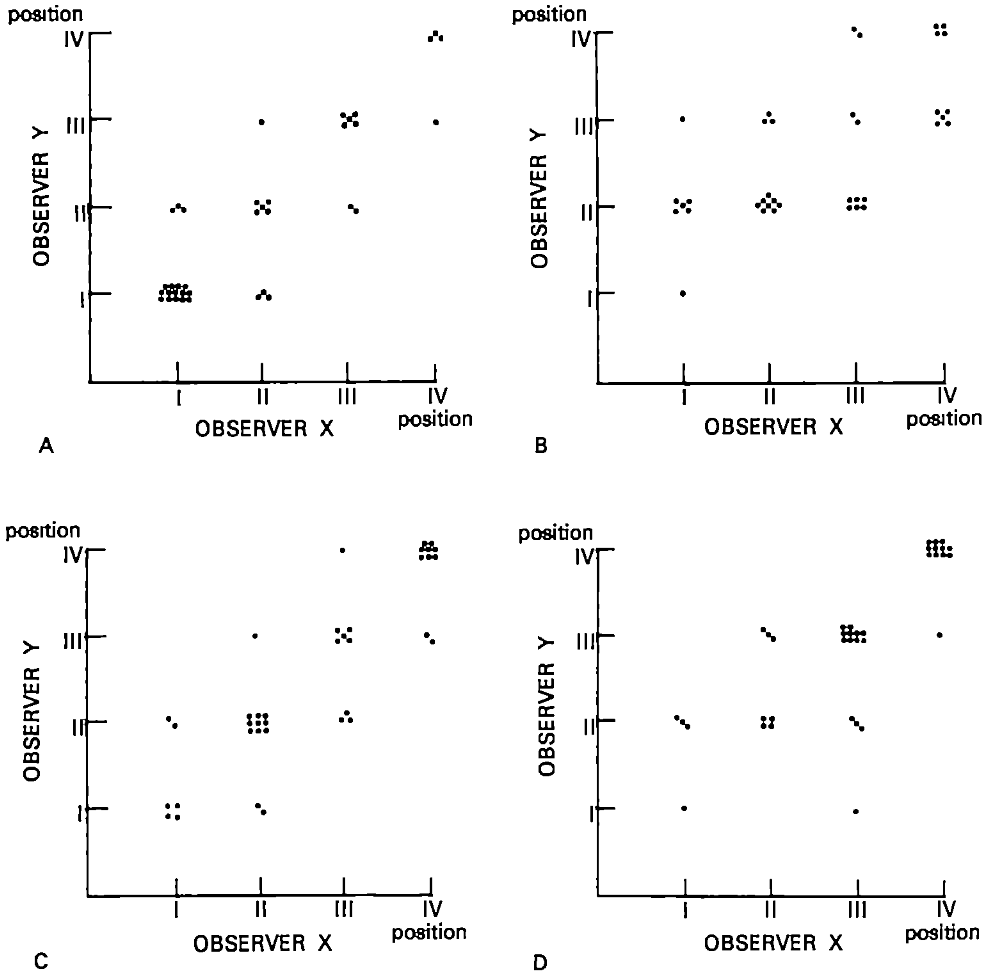

Fig. 1 Relation between observations of observers X and Y. position of testis, n = 37 Scores: non-palpable (I), inguinal (II), high scrotal (III), complete descent (IV). Mean differences between the scores and their standard deviations are quoted in parenthesis. (A) Patient in supine position, right testis (0.1 ± 0.5). (B) Patient squatting, right testis (0.0 ± 0.8). (C) Patient in supine position, left testis (0.1 ± 0.5) (D) Patient squatting, left testis (0.0 ± 0.6)

Table Inter-observer Variation between 2 Observers Examining Position and Motility of Right and Left Testes with Boys in Supine and Squatting Positions

	χ_w	*(95% conf limits)*	$SE_{(\kappa W)}$	$P_{o(w)}$	$P_{e(w)}$	*z (P)*
Position						
Sup. right	0.81	(0.61–1.00)	0.19	0.97	0.83	4.19 (=0.00003)
Squat. right	0.47	(0.16–0.78)	0.16	0.90	0.81	3.01 (=0.00261)
Sup. left	0.86	(0.53–1.00)	0.17	0.97	0.76	5.12 (<0.00001)
Squat. left	0.73	(0.22–1.00)	0.25	0.92	0.70	2.86 (=0.00424)
Motility						
Sup right	0.72	(0.61–0.83)	0.06	0.93	0.74	12.41 (<0.00001)
Squat. right	0.61	(0.28–0.93)	0.16	0.90	0.75	3.74 (=0.00180)
Sup. left	0.75	(0.53–0.97)	0.11	0.93	0.72	6.69 (<0.00001)
Squat. left	0.76	(0.39–1.00)	0.19	0.93	0.71	4.00 (=0.00006)

χ values with 95% confidence limits, standard error ($SE_{(\kappa w)}$), observed agreement rate ($P_{o(w)}$), expected chance agreement rate ($P_{e(w)}$) and critical ratio z with corresponding *P* values.

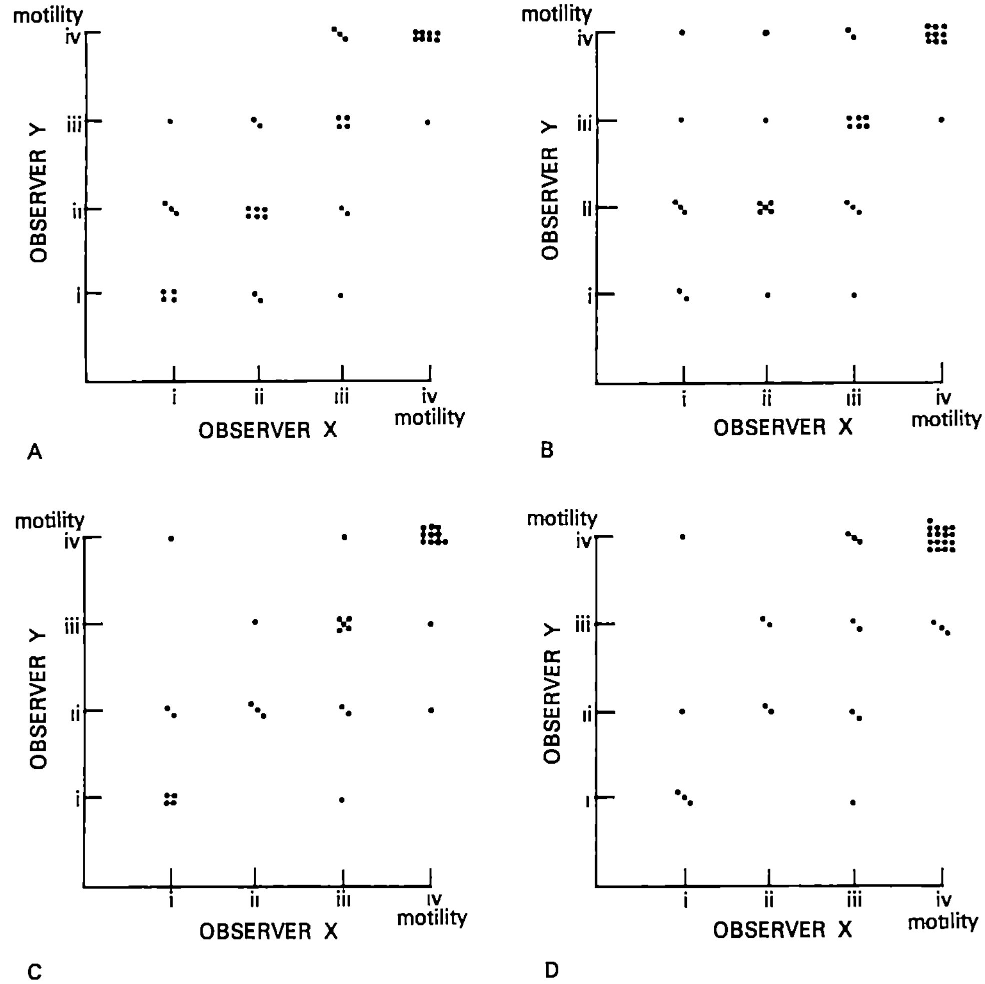

Fig. 2 Relation between observations of observers X and Y. motility of testis, n = 37 Scores: non-mobile (i), hardly mobile (ii), to be manipulated to scrotal entrance (iii), to be manipulated to the bottom of scrotum (iv) Mean differences between the scores and their standard deviations are quoted in parenthesis. (A) Patient in supine position, right testis (−0.1 ± 0.8). (B) Patient squatting, right testis (−0.2 ± 0.9). (C) Patient in supine position, left testis (0.0 ± 0.8). (D) Patient squatting, left testis (−0.1 ± 0.8)

study, since neither observer showed a tendency to record a lower/higher position or lower/higher motility of the testes. Examination with the patient in a squatting position should reduce tension in the subcutaneous tissues and thus increase the incidence of detection. However, the precision of the examination tends to be reduced in this position. The present study indicates that inter-observer variation may be a substantial source of bias in diagnosing the motility and position of undescended testes, in addition to the existing dissent in defining this condition. There is no reason to believe that inter-observer variation would be less at other centres. The use of kappa statistics enables the degree of agreement observed for each sign to be differentiated from the amount of agreement expected from chance alone (Theodossi *et al.*, 1980). When interpreting the kappa values, it should be remembered that apart from being dependent on the extent of observed agreement, values depend on the prevalence of the sign in question in the general population (Kraemer, 1979; Gjørup *et al.*, 1984).

Inter-observer variation, *i.e.* the precision of the diagnosis, may therefore be one explanation for the varying results in reported studies concerning LHRH treatment of undescended testis and the fact that the number of orchiopexies in some countries exceeds the assumed incidence of this condition (Chilvers *et al.*, 1984).

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Case Reports

BCG Pyelonephritis following Intravesical BCG

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Case Report

A 73-year-old man was admitted for radical cystourethrectomy for multiple recurrent superficial transitional cell carcinoma of the bladder. He had been treated by a course of intravesical Epodyl followed by a course of 8 instillations of 120 mg Connaught strain BCG. A preoperative intravenous urogram showed 2 filling defects in the renal pelvis and therefore a left nephroureterectomy was performed at the same time as cystourethrectomy.

Histopathological examination of the nephrectomy specimen showed 2 non-invasive Grade II transitional cell carcinomas. An incidental finding was a wedge-shaped depressed renal cortical scar situated over a dilated calix near the upper pole of the kidney. This was 3 cm in diameter. Histology showed the presence of multiple discrete caseating granulomas (Fig.) which closely mimicked the appearance of tuberculous pyelonephritis, although differing slightly by the occasional presence of calcified Shaumann bodies, scattered foreign-body-type giant cells, and some birefringent crystalline material. Non-necrotising granulomas were noted in the bladder mucosa. No acid-fast bacilli were demonstrable and the patient had no evidence of tuberculosis clinically or on subsequent investigation and follow-up.

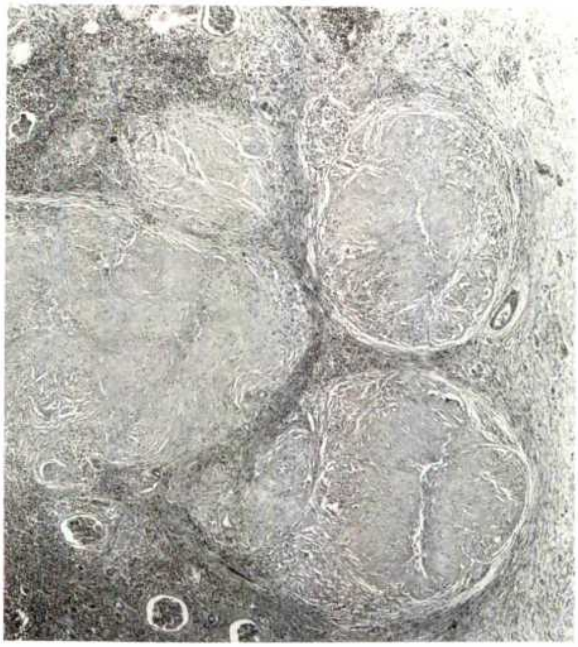

Fig. Discrete necrotising granulomas can be seen in the renal cortex. (H and E ×40).

Comment

Intravesical BCG treatment for transitional cell carcinoma of the bladder may be associated with a variety of systemic and local effects. Granuloma formation following treatment is frequently seen in bladder biopsies (Lage *et al*., 1986) but there are very few reports of involvement of the renal parenchyma (Stanisic *et al*., 1986; Schellhammer, 1987). The mechanism by which the organisms reach the kidney is contentious and a haematogenous pathway has been suggested as being the most likely (Stanisic *et al*., 1986).

The pathological features in our case, in particular the relationship of the lesion to a dilated upper pole calix, strongly suggest a reflux mechanism. Although reflux was not proved pre-operatively, it is likely considering the number of transurethral resections that this patient had undergone which had involved the ureteric orifice. Despite the presence of BCG granulomas in the renal parenchyma, the reflux of BCG into the pelvis was unable to prevent the development of 2 transitional cell carcinomas in the pelvis. Although the lesion in our patient was not clinically significant, its presence suggests that patients with reflux may be at risk of developing BCG pyelonephritis following intravesical BCG therapy.

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Supernumerary Kidney

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Case Report

A 25-year-old man was referred with a 9-month history of urinary frequency. Examination of the abdomen and urine analysis were normal. An IVU showed a low-lying left kidney with a rotated duplex collecting system and duplex ureters, a slightly small but otherwise normal right kidney, and a further area of renal tissue lying at the level of the fifth lumbar vertebra. Four ureters were visualised down to the level of the bladder, 2 on each side. Ultrasound confirmed these findings. A ^{99m}Tc DMSA scan (Fig. 1) revealed the normal right kidney, a large rotated left renal mass, and a supernumerary kidney lying anteriorly on the oblique views. A ^{99m}Tc DTPA renogram (Fig. 2) showed satisfactory drainage from all 4 collecting systems. Cystoscopy revealed only 1 normally positioned ureteric orifice on each side.

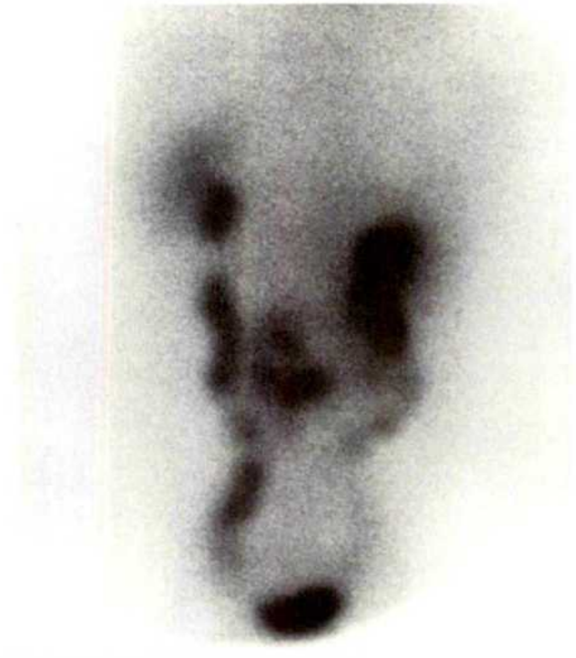

Fig. 2 ^{99m}Tc DTPA scan, anterior view.

Comment

Supernumerary kidney is a rare urogenital anomaly with less than 20 cases reported in the last 20 years. In this case the radiological and isotope appearances raised the possibility that the supernumerary kidney formed part of a horseshoe kidney, which is a particularly unusual association. Diagnosis and follow-up of this condition by radionuclide imaging has only recently been described by Conrad and Loes (1987). A high incidence of complications such as hydronephrosis, stones, pyonephrosis and malignant change has been reported in association with supernumerary kidney and long-term follow-up is advised (N'Guessan and Douglas Stephens, 1983).

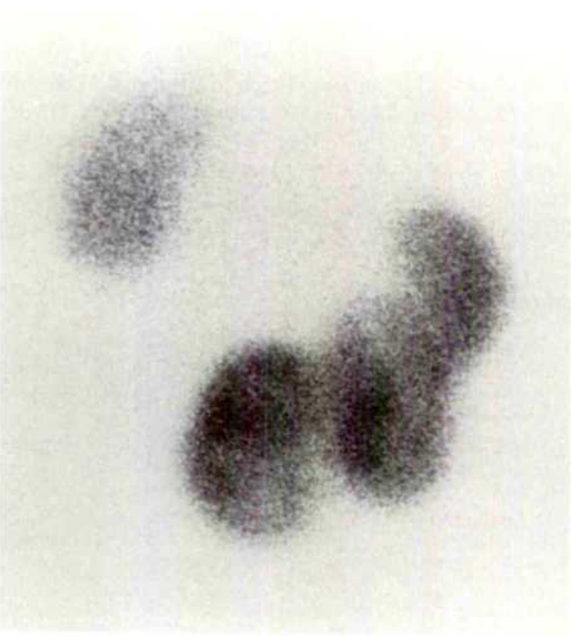

Fig. 1 ^{99m}Tc DMSA scan, anterior view.

Acknowledgements

I thank Dr H. J. Testa, Consultant in Nuclear Medicine, Dr V. Cope, Consultant Radiologist, and Mr E. C. Edwards, Consultant Urologist, for their help in the interpretation of this case.

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Renal Carcinoma with Adjacent Retroperitoneal Fibrosis

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We report the simultaneous occurrence of renal carcinoma and retroperitoneal fibrosis.

Case Report

A previously fit 42-year-old man presented with 1 episode of painless haematuria. He was otherwise well and had taken no medication. Routine blood investigations, including ESR, were normal. Urography, ultrasound and CT scan suggested a large, right renal carcinoma with extracapsular spread and involvement of the renal vein. The vena cava was reportedly patent.

At operation a huge tumour was found, apparently infiltrating colon, liver and diaphragm. Initially, this was considered inoperable but frozen section examination from the limits of the mass demonstrated no malignancy. The tumour was excised through a thoracoabdominal approach.

The kidney contained a yellow tumour measuring 6 cm at the upper pole. Tumour and kidney were surrounded by sclerotic white tissue up to 3 cm in thickness (Fig. 1). The latter consisted of hyalinised fibrous connective tissue, focally infiltrated by lymphocytes, plasma cells and neutrophils. Bands of keloid-like collagenous tissue encircled blood vessels (Fig. 2).

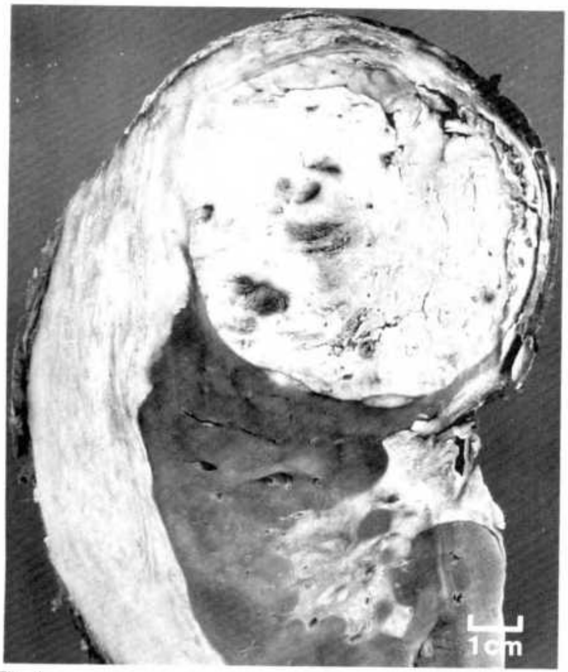

Fig. 1

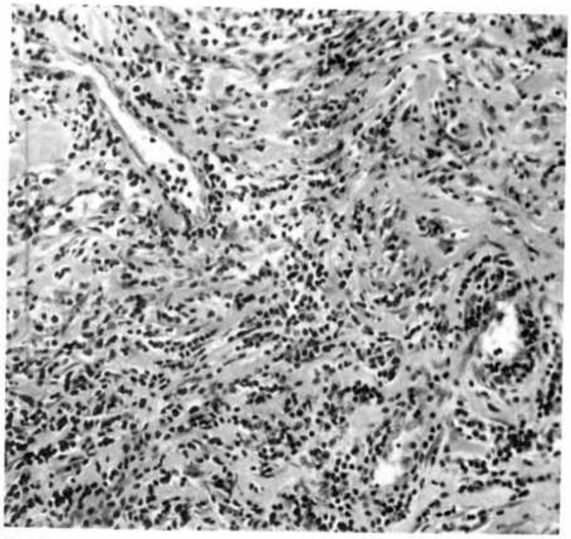

Fig. 2

The appearances were those of retroperitoneal fibrosis.

The tumour was a tubulo-papillary renal carcinoma. The renal capsule showed micro-invasion by tumour cells but there was no tumour in the peri-renal fibrous tissue or renal vein.

Comment

Retroperitoneal fibrosis has been reported in association with tumour of the breast, stomach and urothelium (Ormond, 1960; Webb and Dawson-Edwards, 1967; Thomas and Chisholm, 1973) but not with renal carcinoma. The perirenal fibrosis may have been a response to the carcinoma but no tumour cells were found within this tissue. The clinical lesson is that even in apparently inoperable cases it is worthwhile obtaining frozen section examination and, if benign, persisting with efforts to remove the tumour.

Acknowledgement

We are grateful to Mr R. R. Hall for allowing us to report his patient.

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Subcutaneous Vasopressin in Nocturnal Enuresis

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Synthetic antidiuretics (DDAVP, 1-des-amino-8-D-arginine-vasopressin, Minurin) are increasingly used in the treatment of nocturnal enuresis (Tuvemo, 1978; Aladjem *et al.*, 1982; Nørgaard *et al.*, 1985). We report a case in which the nasal uptake of DDAVP was inadequate but the subcutaneous administration of vasopressin resulted in complete cure.

Case Report

A 32-year-old woman with primary nocturnal enuresis had been unsuccessfully treated with a bell system, tricyclic antidepressants and psychotherapy. Intranasal DDAVP was prescribed and conventional doses (10–40 μg) were initially effective. Soon, however, the effect became intermittent even at high doses (80–100 μg). Urodynamic evaluation was normal except for slight detrusor instability in the standing position and a residual urine volume of 165 ml. The patient's intake of fluid was 1 to 3 l/day and diuresis was 400 to 1500 ml, half of this during sleep. The patient responded normally to fluid deprivation but inconsistently to intranasal Minurin, thus excluding diabetes insipidus. Variable nasal uptake of Minurin was suspected and the subcutaneous administration of vasopressin (10 iu at bedtime) was initiated. On this treatment the patient has been permanently dry at night for 2 months.

Comment

An abnormally low production of vasopressin during the night is considered a major pathogenetic factor in primary nocturnal enuresis (Nørgaard *et al.*, 1985). Intranasal vasopressin at bedtime is therefore a rational treatment to minimise nocturnal urine production. In the present case, diabetes insipidus of hypothalamic or nephrogenic origin was excluded and variable nasal absorption was suspected. It is suggested that subcutaneous vasopressin should be tried in such patients.

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Nephro-broncho-cutaneous Fistula

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Case Report

A 65-year-old woman had suffered 5 years previously from an episode of chills, fever, chest pain, dyspnoea and cough. The diagnosis was empyema and she was treated with antibiotics and thoracic drainage. *Escherichia coli* and *Proteus mirabilis* were cultured from the pleural fluid; 3 weeks later she was asymptomatic and a chest X-ray was normal.

Four years later an abscess in the right flank was drained and formed a sinus with an intermittent purulent discharge. A sinogram (Fig.) showed a nephro-broncho-cutaneous fistula with contrast material in the ureter and in the right bronchial tree. During the examination the patient experienced a severe bout of coughing and complained of a bitter taste in the mouth due to the contrast material. Urine culture yielded *Proteus mirabilis*. IVU revealed a non-functioning right kidney with multiple calculi and a chest X-ray demonstrated right lower lobe infiltration. Ultrasound revealed severe atrophy of the right kidney with a perinephric abscess. Right nephrectomy was suggested but the patient refused operative treatment.

Comment

Nephrobronchial fistula is a rare occurrence (Alvi *et al.*, 1973; Caberwal *et al.*, 1977; Rubin and Morettin, 1982). At times pulmonary complications may dominate the clinical picture and the diagnosis is delayed. The triad of an enlarged kidney, staghorn calculus and ipsilateral posterior basal pulmonary infiltrate is indicative but it is unusual for the fistula

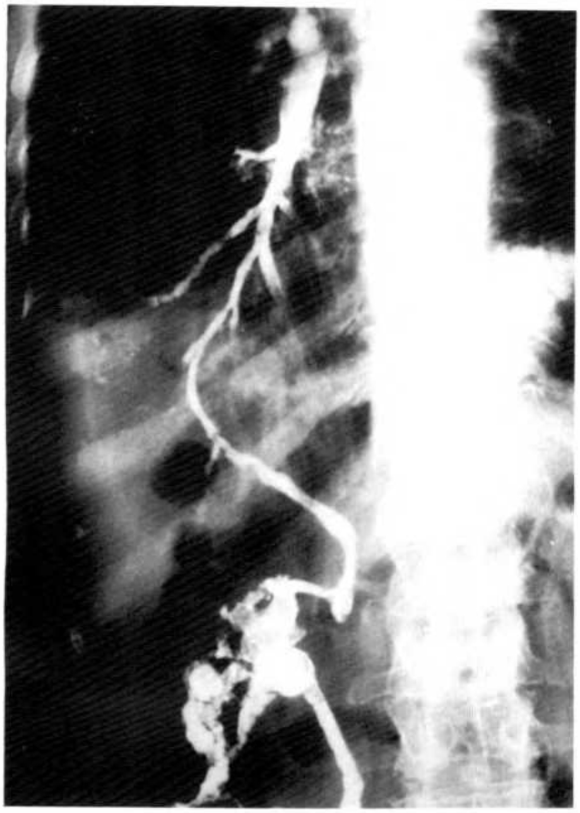

Fig.

to be demonstrated radiographically unless a cutaneous fistula is present and a sinogram can be made.

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Diagnosis and Successful Treatment of *post partum* Renal Vein Thrombosis

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Most cases of adult renal vein thrombosis are associated with the nephrotic syndrome, neoplastic disease and renal transplantation (Clark and Colley, 1980). We present a case of renal vein thrombosis during the puerperium associated with a hereditary coagulation disorder.

Case Report

A 22-year-old woman presented with a 2-day history of malaise, vomiting and left loin pain 2 weeks after stillbirth by Caesarean section. She was acutely tender in the left loin but apyrexial. Blood count showed mild anaemia but no leucocytosis. There was minimal proteinuria and microscopic haematuria and the urine was sterile on culture. An ultrasound scan showed a swollen left kidney but no upper tract dilatation. Intravenous urography showed a delayed and persistent nephrogram on the left side with no contrast excretion. Retrograde ureterography confirmed that there was no evidence of acute obstructive nephropathy. Digital subtraction angiography revealed a patent left renal artery but poor renal perfusion. A CT scan showed an enlarged left kidney which did not enhance well following injection of contrast. There was swelling and oedema around the renal vessels consistent with but not diagnostic of renal vein thrombosis (Fig. 1). Selective renal vein angiography demonstrated complete occlusion of the left renal vein proximal to its junction with the left ovarian vein. An intraluminal thrombus was observed between the ovarian vein and the inferior vena cava (Fig. 2).

The patient was treated with heparin infusion for 2 weeks followed by warfarin. Intravenous urography 6

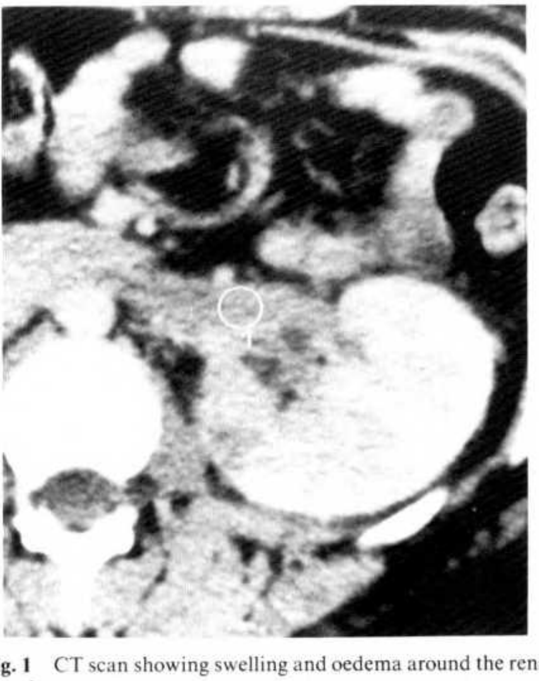

Fig. 1 CT scan showing swelling and oedema around the renal vessels.

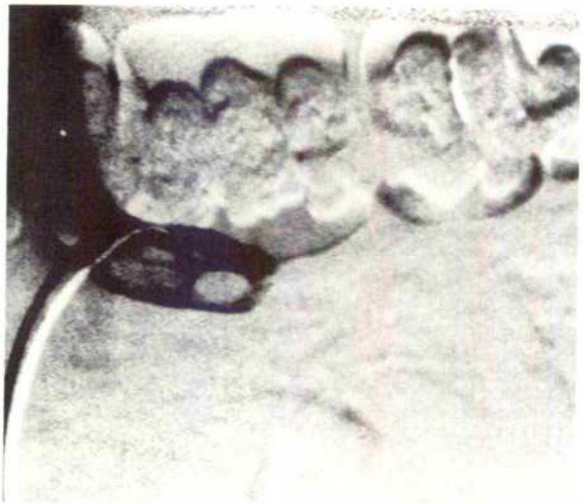

Fig. 2 Selective left renal vein angiogram showing thrombosis within the distal segment.

weeks later showed complete recovery of the left kidney. Subsequent haematological investigation revealed a constant defect in her fibrinolytic system which was similarly demonstrated in her mother and which put her at considerable risk of future thrombotic complications.

Comment

This case illustrates the difficulties in diagnosing acute renal vein thrombosis. Intravenous urograms and ultrasound scans are not able to differentiate between renal vein thrombosis and acute interstitial pyelonephritis. Renal arteriography is rarely diagnostic (Clark and Colley, 1980) and digital subtraction angiography probably provides just as much information and is less invasive. CT scan did not make the diagnosis and this contrasts with the views of other authors (Washecka *et al.*, 1987). Selective renal vein angiography remains the most specific diagnostic test for renal vein thrombosis (Balabanian *et al.*, 1973; Clark and Colley, 1980).

This case demonstrates how important it is to make an early and accurate diagnosis because complete recovery can be expected with instigation of early anticoagulant therapy and this has been confirmed by other authors (Balabanian *et al.*, 1973). Patients with unexplained renal vein thrombosis should be investigated for coagulation disorders.

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Continuous Infusion of Phenylephrine in the Treatment of Papaverine-induced Priapism

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A case of priapism is described which resulted from the injection of papaverine. It failed to respond to conventional pharmacological antidotes but was satisfactorily treated with a continuous intracavernosal infusion of phenylephrine.

Case Report

A 41-year-old male was referred with priapism of 48 hours' duration. He had progressive hereditary spastic paraparesis and had self-injected 80 mg papaverine. Initially he was treated by the aspiration of 50 ml of blood from the cavernosa and the subsequent instillation of 3 mg metaraminol. This produced only a partial response of short duration. Further attempts using bolus injections of 1 mg phenylephrine had a limited effect. An initial dose of 1 mg phenylephrine was given followed by a continuous infusion at the rate of 2 mg/h. This maintained penile flaccidity. The patient's blood pressure was continuously monitored using automatic external monitoring equipment. This regimen was continued for 12 h and following its discontinuation there was no return of the erection.

Comment

Papaverine injected intracavernosally is useful in the diagnosis and treatment of impotence. It is, however, recognised that patients with neuropathic impotence require less pharmacological stimulation to achieve erection.

Priapism is an uncommon yet extremely important complication of the intracavernosal injection of papaverine. Previous reports have demonstrated the usefulness of bolus intracavernosal injections of antagonists such as metaraminol and phenylephrine (Brindley, 1984). Recurrent priapism is often an indication for secondary irreversible operative or embolic procedures (Pryor and Hehir, 1982). In this case the continuous infusion of phenylephrine prevented recurrent priapism. The technique described has several potential side effects related to the cardiovascular properties of phenylephrine. Providing that continuous blood pressure monitoring is used with an automatic alarm device, however, we feel it is a useful therapeutic procedure.

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Liposarcoma of the Bladder

A. D. WIDDISON and R. C. L. FENELEY, *Department of Urology, Southmead Hospital, Bristol*

Non-epithelial tumours of the bladder are uncommon but a liposarcoma appears to be exceptionally rare.

Case Report

A 57-year-old housewife presented with a single episode of painless haematuria. Two years prior to this a right mastectomy had been performed for a multifocal lobular carcinoma. Clinical examination revealed no demonstrable abnormality and the MSU was normal. IVU showed an infundibular stenosis of the middle pole calix and an incomplete obstruction of the distal left ureter. At cystoscopy there was a swelling of the left ureteric orifice giving the appearance of a ureterocele. Biopsy, however, revealed an oedematous wall to the ureter and on bimanual examination there was a palpable sausage-shaped soft swelling 2 to 3 cm long. Histology reported mucosal oedema and chronic inflammation. A laparoscopy was performed to exclude the presence of peritoneal metastasis from the carcinoma of the breast, which was normal. Over the following 6 months she remained free of symptoms and repeat IVU and cystoscopy were unchanged.

The patient then went abroad with her husband, who had a foreign posting. On return to the UK 12 months later she experienced a further episode of haematuria together with increased frequency by day and night. IVU showed an obstructed left ureter and a large filling defect in the bladder (Fig. 1). The tumour in the bladder was resected and histology showed a myxoid liposarcoma (Fig. 2). On bimanual examination a 3 to 4 cm mass was palpable. An *en bloc* resection of the tumour was performed, including the distal end of the left ureter and adjacent bladder. The left ureter was reimplanted into the bladder and a psoas hitch performed. The tumour measured 3.5 × 3.5 × 3.0 cm and was reported as a myxoid liposarcoma replacing the bladder wall and extending proximally adjacent to the left ureter. On review the original biopsy specimen had a similar appearance.

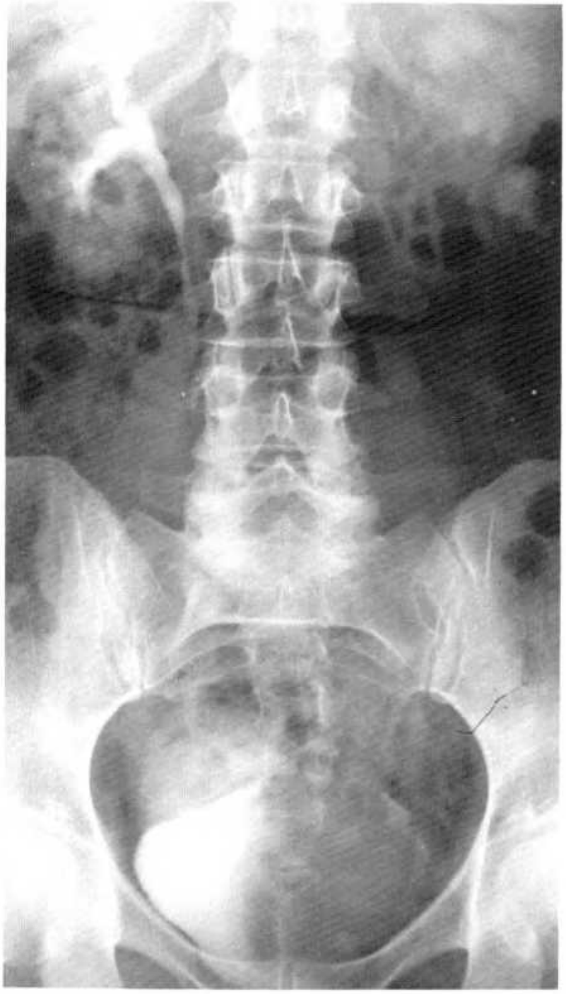

Fig. 1

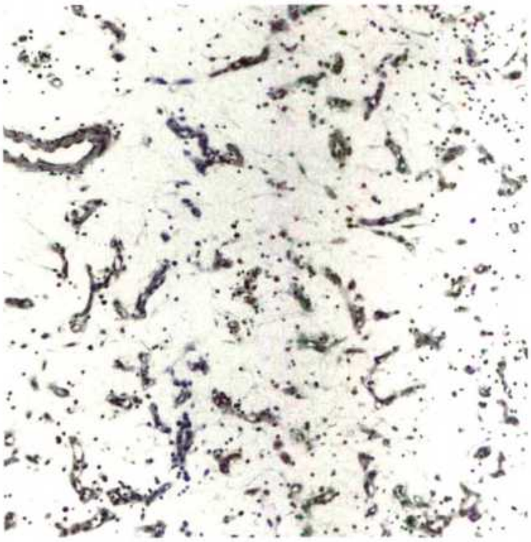

Fig. 2

She made an uneventful post-operative recovery and was well at follow-up 3 months later.

Comment

Liposarcomas account for about 5% of soft tissue tumours and usually present as a large painless mass arising in the lower limbs or from the retroperitoneal tissues (Kindblom *et al.*, 1975; Evans, 1979). Although other sites have been described, only 4 cases of liposarcoma of the bladder have been previously reported. Rosi *et al.* (1983) reported a case of myxoid liposarcoma of the bladder in a 36-year-old man who presented with haematuria. He was alive and well 30 months after a partial cystectomy and pelvic lymphadenopathy with no evidence of recurrence. Sarma (1969) described 3 other cases: a 52-year-old man with a liposarcoma involving the trigone, base and right lateral wall of the bladder who died 1 month later; a 4-year-old boy and a 15-month-old girl who died within a year. However, it is uncertain whether these cases would now be regarded as liposarcomas.

Liposarcomas tend to be slow-growing tumours and patients may have symptoms for many years. Complete *en bloc* resection may be curative, but the prognosis also depends on the size of the tumour, the histology, and the site (Kindblom *et al.*, 1975; Evans, 1979). Small myxoid liposarcomas of the limbs have a better prognosis than larger, poorly differentiated, pleomorphic or round cell liposarcomas arising from the retroperitoneum.

There is a high incidence of local recurrence, particularly if the tumour is large or arising from the retroperitoneum. Further surgery, radiotherapy, or both may give a long-term remission (Kindblom *et al.*, 1975; Evans, 1979). However, the prognosis is independently affected by the delay before recurrence occurs.

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British Journal of Urology (1989), **64**, 657–658

0007–1331/89/0064–0657/$10.00

Points of Technique

Staff Safety and Bladder Irrigation

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Bladder irrigation is commonly used to wash out the bladder following resection of bladder tumours or the prostate. It is also used to clear the bladder of blood and clot in patients presenting with frank haematuria. As a result, large volumes of irrigation fluid mixed with blood, clot and urine require disposal.

Medical practitioners are becoming increasingly aware of the risks to themselves and their colleagues from blood-borne infections, particularly in relation to the human immunodeficiency virus (HIV). If further infection of medical and paramedical staff from patients (Lancet, 1984; Neisson-Vernant *et al.*, 1986) is to be avoided, careful attention must be paid to techniques in dealing with blood or blood-containing fluid from patients.

Technique

In this unit we use the Boots Flowfusor Irrigation System with a 3-way catheter. The irrigation fluid with blood, clot and urine is then drained into a Wallace Cysto-care Unit catheter bag. When the bottle of irrigation fluid is empty it is taken down and replaced by another. The empty bottle is retained as the hole in its lid made by the giving set fits closely around the exit spout of the catheter bag. When the catheter bag is filled to capacity (2 l), its exit spout is placed into the lid of the empty Flowfusor bottle. The length of the spout and the close fit within the lid ensure that when the valve of the Cysto-care bag is opened, the bag empties directly into the bottle without spillage (Fig.). The valve is then closed and the catheter bag is ready to be re-filled. The bottles are subsequently emptied into a sluice.

This method minimises spillage of blood and possible contamination of staff. It is less costly than other systems and avoids the use of sterile measuring jugs. The bottles are graduated and an accurate fluid balance can thus be maintained. In the immediate post-operative period it also allows a visible check on the acceptability of blood staining in the irrigation fluid of successive 2-litre samples.

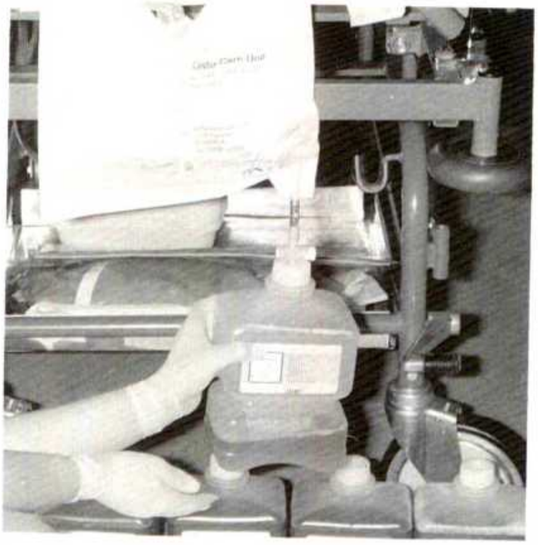

Fig.

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Temporary Upper Tract Urinary Diversion Using a Detachable Occlusion Balloon and Percutaneous Nephrostomy

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Case Report

A 49-year-old woman presented with a stage 4 carcinoma of the cervix which had eroded the bladder and led to a vesico-vaginal fistula. She was treated with radiotherapy but remained incontinent.

The left kidney was non-functioning. The trigone was absent and no ureteric orifices could be seen. In view of the short interval since radiotherapy and the possibility of local tumour recurrence, definitive surgery had to be delayed. Temporary diversion was required to regain both continence and morale.

Technique

Access to the right renal collecting system was achieved percutaneously under local anaesthesia. A detachable 6-mm occlusion balloon was sited at the lower end of the right ureter and the balloon inflated with contrast. An 8F percutaneous nephrostomy pigtail catheter was placed in the right renal pelvis (Fig.).

The patient has remained dry ever since.

Comment

Successful urinary diversion was achieved in this case by a combination of occluding the ureter and percutaneous nephrostomy. Unfortunately, simple nephrostomy alone is insufficient to ensure total upper tract diversion without an adjunctive procedure such as low pressure suction or the use of "superglue" (Gunther *et al.*, 1979; Drury *et al.*, 1983).

The detachable balloon occluding the ureter can be removed ureteroscopically if the fistula heals and the patient is disease-free, or at operation when either definitive surgical upper tract diversion or fistula repair is performed.

Potential complications of this technique include spontaneous deflation of the balloon, leading to recurrent leakage, or ischaemic necrosis of the ureter and subsequent stricture formation due to over-inflation of the balloon (Gordon *et al.*, 1986). These problems were not encountered in this case.

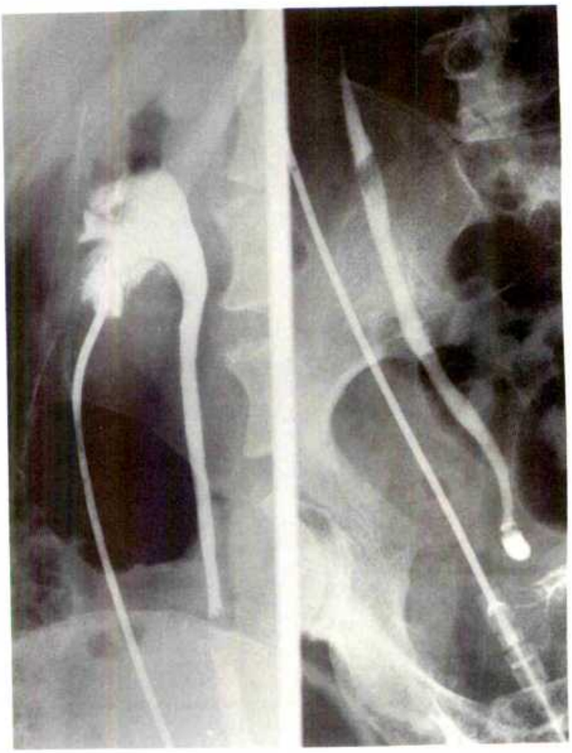

Fig.

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British Journal of Urology (1989), 64, 659–660
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0007-1331/89/0064-0659/$10 00

Correspondence

Dear Sir,

re **Recurrence of superficial bladder carcinoma after intravesical instillation of Mitomycin-C.** A. A. G. M. Giesbers *et al. Br. J. Urol.*, **63**, 176–179, 1989.

The above paper describes a randomised prospective study of 70 patients, comparing exposure times of 0.5 and 1 h respectively of the agent Mitomycin-C (MMC) for the treatment of superficial bladder cancer. However, there are several points concerning the statistical analysis and study design that should be made.

The authors exclude 14 patients (8 from the 0.5 group and 6 from the 1-h group) from the analysis because they did not receive the full course of treatment. Omitting such patients from analysis may seriously bias the analysis since the reason for non-receipt of treatment is likely to be related to the eventual recurrence within a patient.

The effect that exclusion of patients can make to an analysis is illustrated by the following example. Consider the situation that 1 of the patients excluded from the 1-h group and who had a tumour recurrence was added to the 56 patients analysed. This would give the following modified component of Table 3 where the extra patient is indicated in parenthesis.

	Treatment		
Recurrence	*0.5 h*	*1 h*	
Yes	10	4+(1)	14+(1)
No	18	24	42
Total	28	28+(1)	56+(1)

From this modified 2 × 2 table with 57 patients $x^2 = 2.5$ and $P = 0.17$, giving values very different from the reported analysis of 56 patients where $x^2 = 3.4$ and $P = 0.06$. In fact the authors quote an inequality which incorrectly implies $P < 0.05$ for this comparison.

The analysis of recurrences, by means of a 2 × 2 table, is also inappropriate. This is because each patient will have different periods of time before recurrence occurs and "actuarial" or "life-table" analyses of "time to recurrence" should be performed. Such an analysis, whether or not one includes the excluded patients, may give a very different impression of the efficacy of the 2 regimens.

In addition, exclusion from the analysis is particularly worrying when we consider (Table 6A) that all those experiencing toxicity in the 1-h groups were excluded but only 8/18 in the 0.5-h groups.

It is good practice in all trial reports to present the reason for the size of the study and the differences that can be reliably detected with this number of patients. The 35 patients in each treatment arm would only be sufficient (at conventional levels of 5% and 90% for test size and power respectively) to demonstrate a difference in the tumour recurrence rates from (say) 15% in the 1-h group to 55% in the 0.5-h group. Smaller differences would not be reliably detected. It is our view that unless a difference of 40% can reasonably be expected, a trial of this size should not be conducted in this disease. Rather the investigators should make realistic estimates of study size and seek multicentre collaboration for patient recruitment to achieve the necessary numbers.

It seems clear that for a variety of reasons the evidence presented by the authors may *not* be sufficient to conclude "In order to prevent tumour recurrence and to prolong the recurrence interval, a minimum instillation time of 1 h is recommended for patients with superficial bladder carcinoma."

Yours sincerely,

M. K. B. Parmar
Statistician, MRC Cancer Trials Office, 5 Shaftesbury Road, Cambridge CB2 2BW.

Dear Sir,

re **Renal parenchymal malakoplakia.** P. B. Singh *et al. Br. J. Urol.*, **63**, 99–100, 1989.

The underlying abnormality in malakoplakia is defective phagocytosis as a result of low GMP/AMP ratio leading to malfunction of intracellular tubules. Improperly digested bacteria become mineralised, leading to formation of the diagnostic Michaelis-Gutmann bodies (T. Curran. *Br. J. Urol.*, **59**, 559–563, 1987). Nephrectomy has been advocated as the treatment of renal malakoplakia. Bilateral renal parenchymal malakoplakia was found in 7 of 15 cases of renal parenchymal involvement and is invariably fatal (P. A. Deridder *et al. J. Urol.*, **117**, 428–430, 1977). The risk of involvement of the contralateral kidney following unilateral nephrectomy for malakoplakia, though a rare possibility, is unpredictable.

In view of the above facts and its occurrence in a woman in the age group prone to recurrent urinary tract infection, it would seem wise to treat such patients who have undergone unilateral nephrectomy for malakoplakia with an anticholinergic agent, ascorbic acid and an intracellularly active antibiotic (M. J. Stanton and W. Maxted. *J. Urol.*, **125**, 139–141, 1981). This could prevent malakoplakia from affecting the contralateral kidney. Malakoplakia has been known to involve transplanted kidneys (S. B. Streem. *J. Urol.*, **132**, 10–12, 1984) and is associated with high graft loss and mortality rates. Taking into consideration the problems of management of anephric patients in this poverty-stricken continent, where *per capita* health expenditure is only £1.74 per year, all efforts should be directed at conserving renal function.

Yours sincerely,

A. Basu and A. P. Pandey
Department of Urology, Christian Medical College Hospital, Vellore 632 004, India.

British Journal of Urology (1989), 64, 661–662

Prizes and Awards

British Association of Urological Surgeons
President: R. T. Turner-Warwick, DSc, DM, MCh, FRCP, FRCS, FACS

Annual Meeting: St Helier, Jersey, Channel Islands. 20–23 June 1989

St Peter's Medal

At the Annual Dinner the President presented the St Peter's Medal to Professor G. D. Chisholm, ChM, PRCSE, FRCS, after a citation given by Mr J. C. Gingell, FRCS.

BAUS Travelling Fellowship

The 1989 prize was awarded to Mr K. M. Desai for his contributions to Volumes 61 and 62, 1988.

DANTEC Urology Prize

The award for 1988 was given to A. D. Desmond and G. R. Ramayya for the paper entitled "Comparison of pressure/flow studies with micturitional urethral pressure profiles in the diagnosis of urinary outflow obstruction", *British Journal of Urology*, **61**, 224–229.

Surgitek Prize

The 1989 Surgitek Prize was awarded to Mr C. R. Chapple for his paper entitled "Characterisation of human prostate adrenoceptors using pharmacology receptor binding and localisation".

Simpla Research Prize

The 1989 prize was awarded to Mrs Helen F. Parkhouse for the project entitled "A survey of urological symptoms in taxi drivers".

Bard Award

The award for 1989 was given to Mr I. G. Conn for the essay entitled "Prediction of progression in urothelial cancer".

Notices

British Association of Urological Surgeons
President: R. T. Turner-Warwick, DSc, DM, MCh, FRCP, FRCS, FACS

Annual Meeting. Scarborough. 10–13 July 1990

Abstracts of contributions to be considered as either papers, posters or videos by the Programme Sub-Committee of Council should be submitted on the special forms available from the BAUS Secretariat. Completed forms, which should state clearly whether the submission is a paper, a poster or a video, must be returned to the Honorary Secretary by Friday, 5 January 1990.

Abstracts not on the special forms will NOT be considered.

All correspondence to: M. G. Royle, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

European Society of Paediatric Urology

Founded in June 1989, this Society aims to promote paediatric urology by means of clinical co-operation between paediatric urology departments (exchanges, prospective/randomised studies, data banks), research programmes, annual meetings (see Diary page), creation of an autonomous educational training programme and grants for training.

The President is Professor R. Scholtmeijer (Rotterdam), General Secretary Dr P. Mouriquand (Lyon), Treasurer Dr J. de Vries (Nijmegen), and the two Members of the Board are Dr R. Nijman (Rotterdam) and Mr P. Duffy (London).

For further information please contact Dr P. Mouriquand, "Le Dizenier", 11 impasse Mouillard, 69009 Lyon, France.

Bard Award

This award, made possible by the generosity of C. R. Bard International Limited, was given for the first time at the Annual Meeting in Bristol in 1979. The award will consist of the sum of £1500 and the Bard Silver Medal. The award will be given for the best essay submitted specifically for consideration for the award by members of the Association (non-members must be sponsored by a Full Member).

Essays should be based on original work on any topic connected with urological surgery, either clinical or experimental. The essay should include a review of the literature and the clinical implications of the work performed. A panel of three adjudicators will be nominated at the February meeting of Council each year. Submissions for the award should be made in triplicate by 1 March to the Honorary Secretary. The winning essay will be read during the Annual Meeting and should not exceed 20 minutes' duration.

Hans Marberger Prize

The Hans Marberger Prize will be awarded for the first time at the meeting of the German Urological Association in Hamburg in 1990. The prize, which will be donated by Karl Storz Ltd, will amount to öS 50,000 and will be awarded biennially for the best paper in the field of reconstructive surgery in urology or endourology. The award may be split.

Papers may be written in either German or English and should be submitted in triplicate to Dr H. Fuchshuber, Adamgasse 15, A-6020 Innsbruck, by 1 March 1990.

A code word should be affixed to each manuscript, which should not bear the author's name. In a separate envelope bearing the code word the following information should be given: author's first name, surname, position, and code word.

Dantec Urology Prize

An annual prize is awarded by Dantec for the best scientific paper contributing towards the understanding of the function of the urinary tract, which has been accepted by a medical journal for publication in the United Kingdom. Special consideration will be given to papers relevant to clinical human urology. The prize will be known as The Dantec Award for Contribution to the Understanding of Urinary Tract Function. The prize will consist of a £400.00 travel voucher together with a token presentation gift. The prize will be presented at the BAUS Annual Meeting.

The competition is open only to graduates of British or Irish universities resident in the British Isles. Papers which have been published from 1 January to 31 December of the year preceding the award will be considered. Three members of BAUS Council will be nominated at the February meeting of Council to act as adjudicators. All entries, which must include a reprint of the paper in question, must be submitted by 1 April in the year of entry to the Honorary Secretary of the British Association of Urological Surgeons. The winner of the prize will be announced at the Annual Meeting, when the official presentation will be made.

Simpla Research Prize

The Simpla Research Prize was inaugurated in 1988 and consists of an annual prize of £1000.00 to support a clinical research project. Applicants should submit an abstract of not more than 500 words detailing the way in which, if successful, they would use the prize. These submissions should be made to the Honorary Secretary by 1 April. Entries will be judged by three members of Council nominated at the February meeting and the winner will be announced at the Annual General Meeting.

Norwich Eaton Travelling Scholarship

The scholarship(s) will cover travel, accommodation and registration expenses associated with attending the Society of University Urological Residents and American Urological Association meetings. They will be awarded annually until such time as either the Senior Urological Registrars Group or Norwich Eaton Ltd decide not to continue and will be available to any person appointed to an accredited urological training post.

The scholarship(s) will be awarded to the person(s) presenting the winning paper at the Senior Urological Registrars Group Annual Meeting. The winning paper(s) will be selected by those members of the Senior Urological Registrars Group present at the meeting and appointed to urological training posts.

Obituary

James Cosbie Ross, ChM, FRCS, who died on 15 September 1989 at the age of 85, was a founder member of BAUS. He established an artificial kidney unit at Sefton General Hospital in 1959 and this gradually expanded into the Regional Urological Unit, one of the first specialist urology units in the U.K. He made many noteworthy contributions, especially in renal tuberculosis and paraplegia. Cosbie Ross helped to found the Merseyside Association for Kidney Research, he was President of the Liverpool Medical Institution and President of the Moynihan Surgical Club. He was the author of several books, an Associate Editor of Paraplegia and a member of the Editorial Committee of the British Journal of Urology.

British Journal of Urology (1989), 64, 663–664

Diary

1990

January 5	**Closing Date for submission of BAUS abstracts**
January 8–February 2	**Block 2 Diploma Course, Institute of Urology. Contact Course Secretariat, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01 240 9115**
January 12 (SR)	**Guy's Research Meeting—Roden's Suite, Guy's Hospital, London. Details from Mr A R Mundy, Department of Urology, Guy's Hospital, London SE1 9RT. Tel: 01 407 7600**
January 19–20	Video Meeting on Pathology of the Urinary Tract in Children. Lyon, France. Contact Secrétariat du Congrès, Service d'Urologie Pédiatrique, Hôpital Debrousse, 29 rue Soeur Bouvier, 69322 Lyon Cedex 05, France.
January 27–February 3	1990 Winter Urologic Forum Meeting. Steamboat Springs, Colorado, USA. Contact Linda Mace, Staff Assistant, Box 3707, Duke Medical Center, Durham, NC 27710, USA.
March 16	Early Prostatic Cancer—Which Treatment? Newport, Gwent. Contact Mr W. B. Peeling, Department of Urology, St Woolos Hospital, Newport, Gwent NP9 4SZ.
22–24 March	Second European Symposium on Stone Disease. Basel, Switzerland. Contact Mrs W. Heinzelmann, Urologische Klinik der Universität Basel, Spitalstrasse 21, CH-4031 Basel, Switzerland.
March 28–30	**Association of Surgeons of Great Britain and Ireland. Annual Meeting. Cardiff. Closing dates for abstracts 7th October 1989. Contact Ms Caroline Ross at the Royal College of Surgeons, Lincolns Inn Fields, London WC1. Tel: 01 405 3474**
April 22–26	18th Biennial Congress of the Urological Association of South Africa. Durban, South Africa. Contact Uro 1990, P.O. Box 17008, Durban 4013, South Africa.
May 13–17	**Annual Meeting of the American Urological Association, New Orleans. Contact The Secretary, AUA, 1120 N Charles Street, Baltimore, Maryland 21201, USA.**
May 27–June 3	Urological Society of Australasia. 43rd Annual Scientific Meeting Darwin–Kakadu. Contact ASM Secretariat, Urological Society of Australasia, 145 MacQuarie St, Sydney 2000, Australia. Tel: 27 4461
June 1–2	Second International Meeting of Andrology: Diagnosing Male Infertility. New Possibilities and Limits. Como, Italy. Deadline for abstracts: February 28, 1990. Contact Professor G. M. Colpi, II Divisione di Chirurgia, Centro di Andrologia e Infertilità, Ospedale "VALDUCE", Via Dante 11, I-22100 Como, Italy.
June 12	First Annual Meeting of the European Society of Paediatric Urology. Amsterdam, The Netherlands. The topic will be Posterior Urethral Valves. Contact Dr P. Mouriquand, "Le Dizenier", 11 impasse Mouillard, 69009 Lyon, France.

June 13–16	Ninth Congress of the European Association of Urology. Amsterdam. Contact QLT Convention Services, Keizersgracht 792, 1017 AC Amsterdam, The Netherlands. Tel: 010 31 20261372
June 24–28	Canadian Urological Association Meeting, Vancouver, British Columbia, Canada. (To be held jointly with members of BAUS). Contact Dr J. P. Collins, Ottawa Civic Hospital, 1053 Carling Avenue, Ottawa, Ontario K1Y 4E9, Canada.
July 10–13	BAUS Annual Meeting, Spa Conference Centre, Scarborough. Contact Secretariat, Royal College of Surgeons, Lincolns Inn Fields, London WC1. Tel: 01 405 1390
27–30 August	Second Copenhagen Symposium on Uroradiology. Herlev, Denmark. Contact Dr H. S. Thomsen, Department of Diagnostic Radiology 542E, Herlev Hospital, DK-2730 Herlev, Denmark.
12–15 September	International Continence Society: 20th Annual Meeting. Aarhus, Denmark. Contact Dr J. P. Nørgaard, Institute of Clinical Experimental Research, University of Aarhus, DK-8000 Aarhus C, Denmark.

Courses which are recommended for Senior Registrar Education are marked with (SR).

All 'BAUS–associated' meetings/courses are printed in bold.

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